Université de Montréal

Récupération suite à un traumatisme orthopédique avec ou sans traumatisme craniocérébral léger concomitant

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Cette thèse intitulée

Récupération suite à un traumatisme orthopédique avec ou sans traumatisme craniocérébral léger concomitant

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Résumé

Il existe différents facteurs pouvant altérer la récupération fonctionnelle de patients souffrant de traumatismes orthopédiques (TO), dont le fait de subir un traumatisme craniocérébral (TCC) concomitant. Le profil de traumatismes combinés (TCC et TO) a principalement été étudié en contexte de blessures jugées sévères (TCC modéré/sévère et multiples fractures), notamment dans un souci de maximiser la récupération de ces patients et le déploiement des ressources médicales. Par ailleurs, la littérature demeure limitée en ce qui a trait à l'impact de subir un TCC en contexte de blessures jugées moins sévères, soit un TCC léger (TCCL) et une fracture isolée (un seul os fracturé), bien qu'il s'agisse de deux blessures à très forte incidence et qu'elles partagent diverses similarités (p.ex. : mécanismes d'accidents et physiologiques communs). Ainsi, la présente thèse s'est spécifiquement intéressée à cette population aux prises avec une fracture isolée avec, ou sans, TCCL concomitant. Dans un premier temps, les travaux de la thèse ont permis d'investiguer la fréquence de TCCL concomitant en contexte de fracture isolée (article 1) ainsi que son impact sur la récupération post-fracture selon diverses mesures cliniques (articles 2, 3, 4). Les résultats ont démontré que le TCCL était fréquent, quoique fortement sous-diagnostiqué, chez des patients vus au département d'urgence (DU) pour une fracture isolée et que sa présence avait un impact significatif sur le niveau de douleur perçu, le délai pour retourner au travail et le risque de développer de l'ossification hétérotopique (forme de complications orthopédiques). Dans un deuxième temps, la présente thèse a utilisé une approche théorique (article 5) et clinique (article 6) afin d'étudier les mécanismes physiologiques sous-tendant la perception de douleur, symptôme clé suite à une fracture, dans un souci de limiter les risques de chronicisation de la douleur et de proposer des méthodes d'intervention ciblées selon la population étudiée. Les travaux ont notamment mis en lumière une association entre l'intensité de douleur rapportée par des patients en phase aiguë post-fracture et le degré d'atteintes des mécanismes d'excitabilité corticale du cortex moteur primaire mesurées par l'entremise de la stimulation magnétique transcranienne (SMT). Enfin, sur la base d'évidences théoriques soulevées dans un article de revue de la présente thèse, il semble y avoir une pertinence dans l'utilisation de la SMT auprès de la population orthopédique comme méthode d'investigation et d'intervention,

considérant sa capacité à cibler les mécanismes physiologiques impliqués dans la transition de la douleur aiguë à la douleur chronique.

Mots-clés : traumatisme orthopédique, traumatisme crâniocérébral léger, stratégies de dépistage, douleur, profil de récupération, complications orthopédiques, mécanismes physiologiques, stimulation magnétique transcranienne.

Abstract

A variety of factors can affect the functional recovery of patients with an orthopedic trauma (OT), including concomitant traumatic brain injuries (TBI). The recovery profile of patients with combined traumas (OT and TBI) has been studied primarily in the context of severe injuries (moderate/severe TBI and multiple fractures), in order to maximize recovery and medical resources. On the other hand, there is limited evidence on the impact of concomitant TBI in the context of milder injuries, such as in patients sustaining a mild TBI combined with an isolated limb fracture, despite both injuries being highly prevalent and sharing various similarities (e.g., overlapping injury mechanisms and physiological mechanisms). The current thesis sought to bridge this knowledge gap via a multifaceted approach. We first investigated the risk of sustaining a concomitant mild TBI in patients with an isolated limb fracture (article 1) as well as its impact on post-fracture recovery according to various clinical measures (articles 2, 3, 4). The results showed that mild TBI was frequent, although highly underdiagnosed, in patients seeking care for an isolated limb fracture in the emergency department. Moreover, the presence of a concomitant mild TBI had a significant detrimental impact on the level of perceived pain, on return to work delays, and on the risks of developing heterotopic ossification (a type of orthopedic complication). Secondly, this thesis used a theoretical (article 5) and a clinical (article 6) approach to study the physiological mechanisms underlying pain perception, a key symptom following a fracture, in order to limit the risks for pain chronification and to propose intervention methods tailored to the studied population. In particular, results highlighted an association between pain intensity as perceived by patients in the acute phase post-fracture and the degree of cortical excitability impairments of the primary motor cortex, as measured by transcranial magnetic stimulation (TMS). Finally, based on theoretical evidence highlighted in a review article included in this thesis, there are evidence supporting the use of TMS in a traumatically injured population as a method to investigate and intervene given its ability to target key physiological mechanisms involved in the transition from acute to chronic pain.

Keywords: Orthopedic trauma, mild traumatic brain injury, screening strategies, pain, recovery profile, orthopedic complications, physiological mechanisms, transcranial magnetic stimulation.

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Liste des sigles et abréviations

ACRM : American Congress of Rehabilitation Medicine

AINS : Anti-inflammatoires non stéroïdiens

AMPA : A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic

APB : Abducteur pollicis brevis

BBB : Blood brain barrier

BDNF : Brain-derived neurotrophic factor

BHE : Barrière hémato-encéphalique

BMP : Bone morphogenic protein

CDC : Centers for Disease Control and Prevention

CNS : Central nervous system

CRPS : Complex regional pain syndrome

CSR : Conditioning stimulus response

DASH : Disability of the Arm, Shoulder, and Hand

DU : Département d'urgence

DLPFC : Dorsolateral prefrontal cortex

ER : Emergency room

GCS : Glasgow Coma Scale

HO : heterotopic ossification

IASP : International Association for the Study of Pain

ICF : Intracortical facilitation

ICI : Intracortical inhibition

IL-1b : Interleukin-1 beta

IL-6 : Interleukin 6

ILF : Isolated limb fracture

INESSS : Institut National d'Excellence en Santé et en Services Sociaux

ISI : Interstimulus interval

IULF : Isolated upper limb fracture

LICI : Long-interval cortical inhibition

LOC : Loss of consciousness

LTD : Long-term depression

LTP : Long-term potentiation

M1 : Primary motor cortex

MEP : Motor evoked potentials

mTBI : Mild traumatic brain injury

NMDA : N-methyl-D-asparatate

NRS : Numerical rating scale

OT : Orthopedic trauma

rMT : Resting motor threshold

RTW : Return to work

rTMS : Repeated transcranial magnetic stimulation

S1 : Primary somatosensory cortex

S2 : Secondary somatosensory cortex

SICI : Short-intracortical inhibition

SMT : Stimulation magnétique transcranienne

SMTr : Stimulation magnétique transcranienne répétée

SNC : Système nerveux central

SDRC : Syndrome Douloureux régional complexe

TMS : Transcranial magnetic stimulation

TBI : Traumatic brain injury

TBS : Theta-burst stimulation

TCC : Traumatisme craniocérébral

TCCL : Traumatisme craniocérébral léger

TO : Traumatisme orthopédique

TSR : Test stimulus response

À ma marraine Lolo qui m'inspire au quotidien par sa manière

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Chapitre 1 – Contexte théorique

Traumatisme orthopédique

Définition

Il existe différents types de blessures orthopédiques (c.-à-d. fracture, lacération, dislocation), les plus fréquentes étant les fractures, lesquelles se définissent comme étant une rupture de la continuité d'un os pouvant se manifester de différentes façons selon l'atteinte des tissus mous, la localisation anatomique et le nombre de fragments (Claes, Recknagel, & Ignatius, 2012). Une fracture peut être de diverses origines, telles que des suites d'un trauma (blessure traumatique), d'une anomalie du métabolisme osseux ou d'une fragilisation osseuse par une lésion néoplasique (Tintinalli et al., 2016). Le terme traumatique se réfère à toute blessure qui résulte d'un traumatisme franc, direct ou indirect, des suites d'un accident survenant typiquement lors d'une chute, d'un accident de la route (vélo, voiture, etc.), d'une blessure sportive ou de la compression d'un membre (Sheridan et al., 2019). Le traumatisme orthopédique (TO) est le type de trauma le plus fréquemment traité en milieu hospitalier (Urquhart et al., 2006) et correspond à plus de 50% de l'ensemble des blessures vues au DU (Mamaril, Childs, & Sortman, 2007). La présente thèse abordera différents aspects entourant ce type de blessure.

Épidémiologie

Il existe diverses études qui se sont penchées sur le profil populationnel des fractures. Par exemple, en contexte nord-américain, une étude a estimé l'incidence de fractures à 270 par 10 000 individus (Amin, Achenbach, Atkinson, Khosla, & Melton, 2014). L'incidence serait relativement comparable à celle observée en Europe selon une étude réalisée en Suède sur une période de 12 ans qui a dévoilé une incidence de fractures s'élevant à 192 par 10 000 individus (Rosengren, Karlsson, Petersson, & Englund, 2015). Il existe une surreprésentation des femmes (220/10 000) comparativement aux hommes (163/10 000) et la majorité des fractures (77%) provient du squelette appendiculaire (c'est-à-dire tous les os sauf la colonne vertébrale, le bassin, les côtes et le crâne), parmi lesquelles 12%

impliquent une fracture de la hanche (Rosengren et al., 2015). C'est donc dire que la grande majorité des fractures (88%) concerne des os plus périphériques (c.-à-d. fracture aux extrémités du corps). En contexte de trauma musculo-squelettique, le nombre d'os fracturés lors de l'accident tend à varier. Une étude épidémiologique, réalisée par une équipe de recherche en Australie (Urquhart et al., 2006), a comparé en quoi les sujets souffrant d'une fracture isolée différaient démographiquement des personnes victimes de fractures multiples, sans égard aux mécanismes d'accidents (blessure traumatique versus causée par, à titre d'exemple, une anomalie osseuse). Les résultats de cette étude mettent de l'avant que la cohorte atteinte d'une fracture isolée était plus âgée (en moyenne, 60 ans) et plus fréquemment des femmes. Cet impact significatif de l'âge sur le risque de fracture pourrait s'expliquer, du moins en partie, par la fragilisation des os causée par l'ostéoporose (phénomène caractérisé par une diminution de la masse osseuse ainsi qu'une détérioration du tissu osseux) et la perte de la force musculaire, deux conditions étant plus prévalentes chez la femme ménopausée (Ensrud, 2013; Leslie et al., 2020; Rosengren et al., 2015). Ces données suggèrent que l'impact nécessaire pour mener à une fracture isolée peut varier d'un individu à l'autre et ce, en dépit d'un mécanisme d'accident similaire, dépendamment notamment de la vulnérabilité de leurs os. Enfin, sur le plan épidémiologique, il importe de souligner que le type de fractures le plus couramment traité en milieu hospitalier est sujet à des variations saisonnières. En effet, il a été démontré que l'automne et le printemps sont associés à un haut risque de subir des fractures chez les adultes de moins de 50 ans, tandis que le taux de fractures chez les personnes âgées atteint un sommet durant la période hivernale (Hayashi et al., 2019).

Mécanismes d'accident

Les accidents impliquant un véhicule motorisé ou en contexte sportif ainsi que les chutes accidentelles ressortent comme étant les mécanismes d'accident les plus fréquents, surtout les chutes accidentelles en contexte de fractures isolées, selon plusieurs études réalisées en sols nord-américain et européen (Court-Brown & Caesar, 2012; Rosengren et

al., 2015; Sheridan et al., 2019). À plus faible taux, les fractures peuvent également survenir des suites d'une explosion en contexte de guerre ou d'une agression, deux mécanismes d'accident estimés plus communs notamment aux États-Unis (Sheridan et al., 2019; Gordon, Kuhn, Staeheli, & Dromsky, 2015). Il est à noter que la distribution des mécanismes d'accidents traumatiques menant à une fracture est sensible à de multiples facteurs inhérents à chaque pays dont le climat et les enjeux sociodémographiques (Bergstrom, Bjornstig, Stenlund, Jonsson, & Svensson, 2008). Plus spécifiquement au contexte de chutes accidentelles, une étude réalisée en Angleterre a estimé que 60% des fractures surviennent suite à une chute de la hauteur de la victime et que 7% des chutes totales résultent en une fracture (Court-Brown & Bugler, 2012). Encore selon cette étude, 77% des fractures chez les femmes sont causées par des chutes accidentelles, une incidence nettement supérieure à celle des hommes (38%). Il existe également une surreprésentation des fractures du membre supérieur en contexte de chutes, ce qui peut s'expliquer principalement par le mécanisme d'accident impliqué, soit un accident à basse vélocité où la victime est alors souvent portée à se protéger en plaçant les bras vers l'avant pour amortir le choc (DeGoede, Ashton-Miller, Liao, & Alexander, 2001). La rapidité à laquelle la personne réussit à réagir et à se protéger lors d'une chute constitue un facteur étroitement lié aux risques de subir une fracture. Considérant les trois facteurs de risque, soit la fragilité osseuse, l'équilibre précaire et la lenteur à réagir, les personnes âgées sont plus à risque de subir une fracture en contexte de chutes (DeGoede et al., 2001). Par ailleurs, en plus de l'accentuation de la fragilité osseuse liée à l'âge, les femmes seraient également moins aptes à se protéger (moins rapide et musculairement moins fortes) que les hommes, ce qui expliquerait en partie la surreprésentation des femmes dans les statistiques concernant les fractures survenues en contexte de chutes accidentelles (DeGoede et al., 2001). Soulignons que bien que la présente thèse ne porte pas spécifiquement sur ces groupes plus à risque (personnes âgées, femmes), il importe de prendre en considération ces éléments afin d'obtenir un portrait plus juste de la problématique.

Les accidents de la route (voiture, motocyclette, vélo, piéton happé, etc.), survenant typiquement à haute vélocité, constituent également un mécanisme d'accident fréquent pouvant mener à un TO. Une étude de grande envergure menée par Rubin et collègues en 2015 s'est intéressée au risque de subir une fracture chez une cohorte de 71 231 patients hospitalisés suite à un accident de la route (Rubin, Peleg, Givon, Israel Trauma, & Rozen, 2015). Dans un tel contexte, il a été démontré que la plupart des sujets avait subi une seule fracture (78%), dont la majorité (84%) a été répertoriée au niveau de la clavicule, l'omoplate, l'humérus, le radius ou l'ulna, tous des os faisant partie des membres supérieurs du corps. Les résultats montrent également qu'au sein de l'échantillon, 76% des sujets avaient subi des blessures connexes à leur fracture au membre supérieur, dont les plus fréquentes se situaient au niveau de la tête, du cou ou du visage (52%). L'étude a toutefois omis de préciser la nature des blessures connexes (Traumatisme craniocérébral? Contusion? Lacération? Dislocation? Etc.), ne permettant pas d'apporter un plus grand éclairage sur les potentielles blessures concomitantes à surveiller chez cette population ainsi que l'impact de ces blessures sur la récupération de ces patients.

Récupération et pronostic

En suivant le décours naturel de la consolidation osseuse, il est attendu que le patient retrouve un état jugé normal trois à six mois post-accident (Einhorn & Gerstenfeld, 2015). Une consolidation complète, ou une union complète, est achevée lorsque l'os fracturé retrouve une fonction mécanique similaire à celle présente avant la blessure (Jackson & Pacchiana, 2004). Cela se produit grâce à un processus de consolidation remarquable qui implique l'interaction complexe entre différents facteurs mécaniques et biologiques (Stewart, 2019). Les phénomènes associés à la consolidation de l'os ne seront toutefois pas abordés explicitement dans la présente thèse. Au plan clinique, soit au cours du processus de récupération, il est indéniable que les patients expérimenteront une constellation de symptômes post-fractures dont la quantité et l'intensité varient grandement chez chacun. Celles-ci incluent notamment la douleur, une fatigabilité accrue et une atteinte des fonctions motrices du membre fracturé (faiblesses et raideurs

musculaires ainsi qu'une perte d'amplitude articulaire) (McKee et al., 2006), imposant aux patients de réduire leurs activités de la vie quotidienne. Ces manifestations symptomatologiques sont interreliées et font partie intégrante du processus de guérison. À cela s'ajoute la présence de plusieurs facteurs endogènes et exogènes qui peuvent contribuer à optimiser, ou à l'opposé, à ternir le rétablissement de l'individu (Ring et al., 2006; Vranceanu et al., 2014; Hak et al., 2014; Rouleau, Feldman, & Parent, 2009). En ce qui a trait aux facteurs endogènes, l'âge, le sexe (les femmes rapportent typiquement plus de douleur que les hommes), l'état de santé général (comorbidités, embonpoint), la génétique (sensibilité aux stimuli douloureux, risque de développer de la douleur chronique), l'attitude de la personne face à sa condition (isolement versus être engagé dans son rétablissement, expériences passées vis-à-vis la douleur), le degré de catastrophisation, la manifestation d'anxiété et les habitudes de vie (fumeur, mode de vie sédentaire versus actif, etc.) sont reconnus comme pouvant influencer le pronostic de récupération (Ring et al., 2006; Vranceanu et al., 2014). De même, la durée attendue du rétablissement varie selon l'os fracturé, la sévérité de la blessure et l'atteinte concomitante de tissus mous (Einhorn & Gerstenfeld, 2015; Davis et al., 2015). L'accès aux soins, la présence d'un agent payeur ainsi que le recours à la chirurgie ainsi que la technique chirurgicale utilisée constituent des facteurs exogènes influençant le rétablissement du patient (Hak et al., 2014; Rouleau, Feldman, & Parent, 2009).

Malgré les traitements et les suivis offerts par l'équipe médicale (orthopédistes, physiatres, infirmière, etc.) ainsi que par les professionnels paramédicaux (physiothérapeutes, ergothérapeutes, chiropraticiens, etc.), certains patients développeront des complications (Claes et al., 2012; Hanson, Neidenbach, de Boer, & Stengel, 2009; McKee et al., 2006; Rosengren et al., 2015; Urquhart et al., 2006). Les complications orthopédiques regroupent un amalgame de symptômes qui persistent au-delà de la période de récupération attendue, incluant notamment les faiblesses musculaires, la fatigabilité accrue, la perte d'amplitude articulaire et la douleur. Ces symptômes s'avèrent tous incapacitants pour les individus touchés qui souffrent depuis déjà plusieurs semaines, voire plusieurs mois. L'origine des déficits fonctionnels est

variable. Il a notamment été suggéré qu'un défaut au niveau du processus physiologique sous-tendant la consolidation osseuse, naturellement enclenché dès la fracture de l'os, soit à l'origine des complications orthopédiques (Einhorn & Gerstenfeld, 2015). Cela se traduit notamment par un délai d'union (retard au niveau de la consolidation de l'os), une non-union (absence de consolidation de l'os), une mal-union (consolidation anormale de l'os) ou par de l'ossification hétérotopique (développement d'une structure osseuse anormale dans les tissus mous) (Andrzejowski & Giannoudis, 2019; Kostenuik & Mirza, 2017; Meyers et al., 2019). Concernant l'ossification hétérotopique, qui sera abordée plus spécifiquement dans cette thèse, l'incidence varie étroitement selon le type de fracture, pouvant se retrouver chez jusqu'à 40% des patients souffrant d'une fracture du coude (Eisenstein, Stapley, & Grover, 2018; Foruria, Augustin, Morrey, & Sanchez-Sotelo, 2013; Foruria, Lawrence, Augustin, Morrey, & Sanchez-Sotelo, 2014). Les répercussions fonctionnelles de la formation d'ossification hétérotopique sont des contractures articulaires, des séquelles motrices ainsi que des sensations douloureuses, pouvant devenir une condition débilitante pour les patients affectés (Vanden Bossche & Vanderstraeten, 2005). Dans ce contexte, une intervention chirurgicale pour exciser l'ossification est souvent requise afin de minimiser l'impact fonctionnel (amplitude articulaire, faiblesse musculaire, fatigabilité accrue, etc.) et de prévenir l'apparition de séquelles difficilement réversibles (douleur chronique, etc.).

Douleur

En plus des atteintes fonctionnelles, la douleur aiguë, faisant partie intégrante du processus de consolidation, est pratiquement inévitable suite à une fracture et représente la principale plainte chez la population orthopédique (Krauss, Calligaris, Green, & Barbi, 2016; Platts-Mills et al., 2016). Celle-ci, rapportée par non moins de 70% à 97% des patients ayant subi un trauma, affecte considérablement non seulement la qualité de vie des patients, mais peut également nuire au rétablissement orthopédique (Albrecht et al., 2013; Archer, Castillo, Wegener, Abraham, & Obremskey, 2012). On peut donc affirmer que la douleur joue un rôle important dans la récupération fonctionnelle

d'un patient. En effet, la douleur influence le degré d'investissement du patient dans son rétablissement, de sorte qu'un patient en douleur tend à être moins investi dans le processus de guérison, et donc, devient plus enclin à récupérer plus tardivement (Majuta, Longo, Fealk, McCaffrey, & Mantyh, 2015).

Dans certains cas, la douleur aiguë se transforme en douleur chronique, soit lorsque celle-ci persiste au-delà de trois mois post-accident (Ydreborg, Engstrand, Steinvall, & Larsson, 2015), devenant donc un enjeu majeur pour les professionnels qui prodiguent les soins. En effet, lorsque la douleur devient chronique, il arrive que celle-ci se diffuse et déborde de la zone initiale de la blessure, ou même augmente en intensité, devenant donc plus invalidante et plus difficilement traitable (Howland, Lopez, & Zhang, 2016). Dans certains cas, le développement de l'état de douleur chronique s'explique par un facteur mécanique, découlant, par exemple, d'une fracture non guérie (c.-à-d. mal-union/non-union) ou encore d'une infection profonde post-opératoire (Egol, Gruson, Spitzer, Walsh, & Tejwani, 2009; Friesgaard et al., 2016). Or, pour la majorité des cas, il n'y a pas de cause mécanique identifiable. Dans ce contexte, la douleur chronique découle de deux facteurs, soit la sensibilisation centrale et la neuroinflammation (Oostinga, Steverink, van Wijck, & Verlaan, 2020). Ces mécanismes clés de la douleur chronique ont été abordés dans un article de revue de la présente thèse (voir article 5) et seront donc brièvement résumés dans la présente section. La sensibilisation centrale est une atteinte du système nerveux central (SNC). Habituellement, la réponse nociceptive au site de la blessure génère de l'activité excitatrice qui est maintenue localement, soit à proximité du site de la blessure dans le système nerveux périphérique, sans atteindre le SNC. Par contre, lorsque l'activité excitatrice devient anormalement élevée, soit en raison d'un état lacunaire des mécanismes compensatoires (mécanismes inhibiteurs) ayant normalement une utilité fondamentale pour maintenir l'homéostasie, celle-ci peut atteindre le SNC (Clauw, 2015; Hanakawa, 2012; McGreevy, Bottros, & Raja, 2011). Plus spécifiquement, on note, au plan physiologique, une hyperactivité dans le SNC des récepteurs glutamatergiques N-methyl-D-aspartate (NMDA; principal marqueur d'excitabilité dans le SNC) et une hypoactivation de l'activité GABA (principal marqueur d'inhibition dans le SNC) (Baba et al., 2003;

Latremoliere & Woolf, 2009). Cette hyperactivité du SNC génère une augmentation de l'activité excitatrice maladaptive dans la moelle épinière et le cerveau, ce qui facilite la transmission de la douleur émanant du site de la blessure (fracture) en périphérie jusqu'au cerveau. En somme, ce débalancement physiologique a pour effet d'altérer le traitement des signaux douloureux et/ou non-douloureux (Naro et al., 2016; Petrenko, Yamakura, Baba, & Shimoji, 2003).

La neuroinflammation s'explique, pour sa part, par une altération du processus naturel de résorption de la réponse inflammatoire enclenchée par la blessure. Ainsi, tout comme pour la sensibilisation centrale, si la réponse inflammatoire prend de l'ampleur, elle peut atteindre le SNC (Schinkel et al., 2006). Plus spécifiquement, les cytokines pro-inflammatoires (TNF-a, IL-6 et IL-1b), présentes au moment de la blessure, jouent un rôle majeur dans la chronicisation de la douleur (Galic, Riazi, & Pittman, 2012). En effet, il y a une augmentation significative des cytokines pro-inflammatoires qui, ensuite, agissent surtout comme médiateurs sur l'activité des neurotransmetteurs du SNC, en augmentant l'activité glutaminergique et en diminuant l'activité GABAergique (Watkins, Milligan, & Maier, 2003; Zhang & An, 2007). Ainsi, l'augmentation des cytokines pro-inflammatoires altère d'autant plus l'homéostasie du SNC et alimente les mécanismes de sensibilisation centrale.

Une façon de mesurer l'activité glutamatergique et GABAergique est la stimulation magnétique transcrânienne (SMT). Il s'agit d'une technique de stimulation non invasive du cerveau qui permet de mesurer l'activité des neurones, soit l'excitabilité corticale, situés dans un champ magnétique précis, déterminé par la région cérébrale stimulée. Brièvement, la SMT fonctionne selon le principe d'induction électromagnétique, à savoir que le champ magnétique induit par la bobine génère un courant électrique au moment d'atteindre la région cible (Bashir, Mizrahi, Weaver, Fregni, & Pascual-Leone, 2010). Son utilité en contexte de douleur a été démontrée depuis des décennies, ayant offert aux experts du domaine une meilleure compréhension de la façon dont le SNC (le cerveau ainsi que les voies ascendantes et descendantes) intègre et réagit lors d'une expérience

douloureuse. Par exemple, plusieurs études ont démontré que la douleur aiguë induite expérimentalement chez des sujets sains exerce une influence inhibitrice (augmentation de l'activité GABA) sur l'excitabilité cortico-spinale (stimulation du cortex moteur primaire) (Le Pera et al., 2001; Svensson, Miles, McKay, & Ridding, 2003; Valeriani et al., 2001; Valeriani et al., 1999). Par ailleurs, ce profil inhibiteur serait inversé lorsque la douleur se chronicise, donnant place à une augmentation de l'activité glutaminergique, ce qui est compatible avec les mécanismes de sensibilisation centrale décrits précédemment. L'augmentation de l'activité glutaminergique accentue l'activité excitatrice au niveau des réseaux nocicepteurs du système nerveux central. Ainsi, la SMT s'avère pertinente pour évaluer une partie des mécanismes potentiellement impliqués dans la chronicisation de la douleur.

Mesures de l'état fonctionnel

Il existe diverses méthodes pour suivre l'évaluation fonctionnelle de patients atteints de fractures. Seules celles pertinentes aux études de la présente thèse seront abordées dans cette section. Les mesures autorapportées, telles que les questionnaires, sont souvent utilisées comme point de référence notamment en raison de leur valeur écologique. Le questionnaire DASH (Disability of the Arm, Shoulder, and Hand) est communément utilisé chez la population victime de fractures aux membres supérieurs (Angst, Schwyzer, Aeschlimann, Simmen, & Goldhahn, 2011; Gummesson, Atroshi, & Ekdahl, 2003). Ses questions permettent de mesurer l'impact de la blessure sur la capacité de la personne à réaliser diverses activités de la vie quotidienne (cuisiner, faire son lit, faire son travail, etc.). L'échelle visuelle analogique de douleur ou l'échelle numérique de douleur sont également deux outils de référence classiques qui sont simples d'utilisation et qui permettent de suivre l'évolution de la douleur à différents stades de la récupération post-fracture (Downie et al., 1978; Williamson & Hoggart, 2005). Il a même été démontré que ces mesures, lorsque recueillies en phase aiguë, peuvent servir de prédicteur quant au risque de chronicisation des symptômes douloureux (Apkarian, Baliki, & Farmer, 2013). Qui plus est, des corrélations entre les résultats issus de ces questionnaires et de mesures objectives (p.ex. : force de préhension, amplitude articulaire, trouvailles radiologiques,

etc.) ont été démontrées dans la littérature, appuyant à nouveau leur utilité clinique (Karnezis & Fragkiadakis, 2002; Wilcke, Abbaszadegan, & Adolphson, 2007).

Le retour au travail s'avère également un bon indicateur de la condition générale du patient travailleur suite à une fracture, servant de mesure pour comparer le fonctionnement des individus à celui qu'ils avaient avant l'accident (Clay, Newstead, & McClure, 2010). Dans une revue de littérature publiée par Clay et collègues (2010), les facteurs tels que le jeune âge, l'état de santé, la sévérité de la blessure, et l'absence de compensation financière ont été identifiés comme facteurs favorisant un retour au travail précoce. Au-delà des facteurs favorisant un retour au travail, il est attendu que la majorité des sujets ayant subi une fracture isolée réussisse à réintégrer un emploi post-convalescence. En effet, une étude a montré que 85% des individus ayant subi une fracture aux extrémités (membres supérieur ou inférieur) étaient retournés au travail dans les six mois suivants l'accident (Hou, Tsauo, Lin, Liang, & Du, 2008). Parmi ceux-ci, 78% avaient réintégré le même emploi pré-accidentel. Néanmoins, certains individus ne réussissent pas à retourner au travail et se chronicisent en dépit de l'absence de motifs médicaux évidents. Un retard au niveau du retour au travail déborde des impacts directs de la blessure physique, étant associé à des facteurs psychologiques (isolement social, anxiété, dépression, etc.) et sociaux (pertes financières, etc.) (O'Hara, Isaac, Slobogean, & Klazinga, 2020).

Traumatisme craniocérébral

Définition du TCC

Un traumatisme craniocérébral (TCC) est une atteinte cérébrale causée par une force mécanique externe, directe ou indirecte, vers le crâne et les structures sous-jacentes, provoquant une altération immédiate du fonctionnement normal du cerveau (Menon et al., 2010). Celui-ci peut être causé par une blessure ouverte (pénétrante), responsable de 40% des décès suite à un TCC, ou fermée (non pénétrante) (Coronado et al., 2011). Cette dernière, beaucoup plus fréquente, est causée par un mouvement brusque

(accélération/décélération/rotation) provoquant un contact entre le cerveau et la boite crânienne et engendrant un transfert d'énergie cinétique. Les séquelles qui en découlent ne sont pas nécessairement proportionnelles à la force à laquelle le cerveau se heurte contre la boite crânienne (Menon et al., 2010), car plusieurs facteurs influencent le pronostic. Par exemple, l'âge, le mécanisme d'accident, le niveau d'éducation, la présence de blessures concomitantes et d'antécédents psychiatriques, ainsi qu'un historique de TCC, sont identifiés comme un ensemble de facteurs pouvant altérer le rétablissement (Lingsma et al., 2015).

Sévérité

La sévérité du TCC est déterminée par l'étendue et l'ampleur des manifestations cliniques, telles l'altération de l'état de conscience (perte de conscience/confusion), l'amnésie post-traumatique ainsi que la présence de lésions intracrâniennes et de signes neurologiques (signes focaux, convulsions, vomissements). Le Glasgow Coma Scale (GCS) est une échelle d'évaluation symptomatique permettant de mesurer l'état de conscience du patient en phase aiguë en plus d'évaluer la sévérité du TCC en établissant un score entre 3 (coma profond) et 15 (parfaitement conscient et orienté) (Teasdale & Jennett, 1974). Le TCC sévère se caractérise par un score variant entre 3 et 8 au GCS et est associé à une perte de conscience de plus de 24 heures et à une période d'amnésie post-traumatique de plusieurs semaines (Carroll et al., 2004). Le TCC modéré (score entre 9 et 12 au GCS) implique, quant à lui, une perte de conscience de 30 minutes à 24 heures ainsi qu'une amnésie post-traumatique généralement de 1 à 14 jours. Finalement, le TCC léger (TCCL) (score entre 13 et 15 au GCS) cause une perturbation transitoire de l'état de conscience dont la durée est inférieure à 30 minutes (avec ou sans perte de conscience) ainsi qu'une amnésie post-traumatique d'une durée maximale de 24 heures. Le TCCL peut ensuite être catégorisé selon les résultats obtenus à l'examen neuroradiologique ainsi que le contexte entourant l'accident. Par exemple, le diagnostic de TCCL simple est donné lorsque le scan ne révèle aucune anomalie cérébrale (scan négatif), alors qu'un diagnostic de TCCL complexe est retenu lorsque le scan démontre la présence de lésions cérébrales (scan positif), mais ne nécessitant pas le recours à une intervention chirurgicale. Cette

distinction est seulement faite au Québec, l'appellation du TCCL complexe n'existant pas ailleurs. Par ailleurs, il est à noter que cette classification du TCCL n'a aucun pouvoir prédictif sur le pronostic. Finalement, le terme « commotion cérébrale », qui survient, par définition, exclusivement dans un contexte sportif, est souvent utilisé de façon interchangeable avec le TCCL en raison de la similarité des symptômes, étant même souvent rapporté comme un TCCL d'origine sportive (McCrory, 2013).

Incidence

Le TCC serait le trouble neurologique le plus fréquent après les maux de tête, atteignant une incidence supérieure à celle combinant la maladie de Parkinson, la sclérose en plaques, le syndrome de Guillain-Barré, la sclérose latérale amyotrophique et la myasthénie (Daoudi, Langlois, Muller, Dacher, & Pfister, 2006; Kiraly & Kiraly, 2007). Une étude récente d'envergure mondiale a recouru aux données recueillies par le World Health Organization et le World Bank afin d'estimer l'incidence globale des TCC (Dewan et al., 2018). Cette étude révèle, qu'au total, il y aurait un peu plus de 69 millions de nouvelles victimes de TCC par année à travers le monde, soit un ratio de 939 par 100 000 habitants. Plus spécifiquement, cette étude estime à 1 299 par 100 000 habitants le nombre de nouveaux cas annuellement aux États-Unis/Canada (Dewan et al., 2018). Notons toutefois que les projections canadiennes se sont faites à partir des données américaines de sorte que ces données doivent être interprétées avec précaution étant donné les différences populationnelles. Les auteurs de l'étude précisent que l'écart entre l'incidence de la région nord-américaine par rapport à l'incidence mondiale s'explique, en partie, par l'absence de données robustes et le manque de ressources dans certains pays notamment ceux du tiers monde. Environ 81% des TCC seraient de grade léger, ce qui, selon Dewan et collègues (2018), correspond à plus de 55 millions de nouveaux cas annuellement. Une autre étude a plutôt estimé à 42 millions l'incidence annuelle de TCCL (Gardner & Yaffe, 2015), une différence statistique qui semble surtout tributaire de la divergence dans l'approche méthodologique préconisée entre les deux études. Enfin, en raison du faible taux de consultation à la suite d'un TCCL et des nombreux cas qui ne sont

pas documentés dans les archives médicales, les experts estiment que l'incidence annuelle serait en fait beaucoup plus élevée que ce que la littérature laisse présager (Cancelliere et al., 2014).

Types et mécanismes d'accident

Selon la CDC, les TCCL surviennent typiquement à la suite de chutes accidentelles (28%), d'accidents de la route (20%), d'accidents résultant d'un contact direct à la tête (19%) ou d'un assaut (11%) (Centers for Disease Control and Prevention, 2011). Il a été suggéré qu'un mécanisme d'accident impliquant un contact de type accélération/décélération augmente significativement le risque de subir un TCCL en raison du transfert d'énergie cinétique pouvant être provoqué subséquemment (Stuart, Mandleco, Wilshaw, Beckstrand, & Heaston, 2012). Par ailleurs, les forces rotationnelles, souvent engendrées par une collision, seraient en fait les plus dommageables en raison du risque accru d'effritement des axones (Blennow, Hardy, & Zetterberg, 2012; Kiraly & Kiraly, 2007; MacFarlane & Glenn, 2015).

Physiopathologie

Dans le cas du TCCL, il existe deux types de dommages (c.-à-d. blessure primaire et blessure secondaire) qui varient selon la nature, l'intensité, la direction et la durée des forces au moment de l'impact (Werner & Engelhard, 2007). En premier lieu, la blessure primaire résulte de l'application des forces mécaniques contre le crâne au moment de l'impact et peut entrainer plusieurs types de séquelles, dont des lésions locales (fractures du crâne, hématomes intracrâniens, lacérations, contusions) et, de manière plus rare en contexte de TCCL, des lésions diffuses (Greve & Zink, 2009). Ensuite, la blessure secondaire, provient, quant à elle, de la réponse cellulaire, telle l'hypoxie cellulaire, pouvant provoquer des séquelles qui tendent à prendre plus de temps à se manifester. En effet, le TCCL produit une cascade neurométabolique complexe qui, à son tour, compromet l'équilibre physiologique et cause un débalancement entre le transport d'oxygène aux neurones et la consommation cérébrale en oxygène (Blennow et al., 2012;

MacFarlane & Glenn, 2015). Spécifiquement, ce débalancement est provoqué par une libération incontrôlée d'ions (sodium/potassium et calcium) intracellulaires vers l'extérieur de la cellule ainsi qu'une augmentation extracellulaire de neurotransmetteurs excitateurs (glutamate et aspartate) (MacFarlane & Glenn, 2015). Comme les pompes ioniques dépensent énormément d'énergie en essayant de retrouver une homéostasie cellulaire, le cerveau subit une crise énergique (épuisement neuronale) qui survient de surcroît dans un contexte de réduction du flot sanguin cérébral, ce dernier étant altéré compte tenu du lien étroit qu'il entretient avec l'activité neuronale (Giza & Hovda, 2001). Une cascade neuroinflammatoire fait également partie des mécanismes impliqués dans la blessure secondaire (Loane & Faden, 2010) et serait, selon la littérature, tributaire des perturbations au niveau de la membrane neuronale et de la barrière hémato-encéphalique (BHE) (Johnson et al., 2018; Wofford, Loane, & Cullen, 2019). La réaction inflammatoire, pouvant durer plusieurs jours voire des mois, est un processus complexe, impliquant, notamment, une activation significative de la microglie (Wofford et al., 2019)). De par sa fonction, la microglie devient activée seulement lorsqu'une menace ou un dommage sont détectés au niveau du SNC (Nimmerjahn, Kirchhoff, & Helmchen, 2005). L'activation de la microglie provoque ensuite la libération de médiateurs (cytokines) responsables de deux fonctions distinctes, voire contradictoires, soit de neuroprotection (processus anti-inflammatoire) et de neurodestruction (processus toxique et pro-inflammatoire) (Block, Zecca, & Hong, 2007; Nimmerjahn et al., 2005; Witcher, Eiferman, & Godbout, 2015). L'équilibre entre les volets neuroprotecteur et neurodestructeur est précaire, de sorte que lorsqu'un débalancement entre ces deux mécanismes survient à l'avantage du second, des symptômes cliniques se manifestent (Gao & Hong, 2008).

Ainsi, dans l'ensemble, ces mécanismes menant au dysfonctionnement cérébral post-TCCL seraient en partie responsables des déficits cognitifs et des symptômes post-commotionnels observés à la suite d'un TCCL (MacFarlane & Glenn, 2015).

Diagnostic de TCCL

Le diagnostic de TCC se base généralement sur les résultats obtenus à l'examen neuroradiologique, les symptômes rapportés ainsi que le score au GCS, tel qu'établi par les premiers répondants (Albicini & McKinlay, 2014; Buck, 2011). Contrairement aux TCC sévères et modérés, les professionnels médicaux ne peuvent compter exclusivement sur les résultats radiologiques pour établir un diagnostic de TCCL, car seulement 10% des victimes présentent des lésions cérébrales traumatiques aux examens neuroradiologiques conventionnels (p.ex. : CT Scan) (Dhawan, Rose, Krassioukov, & Miller, 2006). Depuis plusieurs années, les cliniciens et les chercheurs travaillent d'arrache-pied pour implanter une procédure standardisée qui vise à réduire les cas de TCCL non diagnostiqués en identifiant les personnes à risque et en effectuant le dépistage le plus juste et efficace possible (McCrory, 2013; Prince & Bruhns, 2017). L'identification précoce des TCCL est fondamentale considérant que l'absence de diagnostic mène à une absence d'intervention de la part des professionnels de la santé et augmente ainsi les risques de chronicisation des symptômes (Powell, Ferraro, Dikmen, Temkin, & Bell, 2008). Par ailleurs, malgré les récents efforts, le TCCL demeure particulièrement difficile à dépister en raison du faible taux de consultation (on estime à 25% la proportion d'individus ne consultant pas suite à un TCCL) et de la difficulté à reconnaitre les symptômes (Buck, 2011; Iverson, 2005; Kashluba, Hanks, Casey, & Millis, 2008; Ryu, Feinstein, Colantonio, Streiner, & Dawson, 2009). Une étude récente estime que 50% à 90% des TCCL ne sont pas identifiés chez des patients consultant les services d'urgence post-accident (McCrea, Nelson, & Guskiewicz, 2017). Un des facteurs contribuant au faible taux d'identification du TCCL est le haut débit de clientèle fréquentant les services d'urgence ce qui fait en sorte que les soins sont souvent accordés en priorité aux patients se trouvant dans un état critique ou atteints de blessures visibles. Ainsi, il est possible que les symptômes non visibles et parfois non spécifiques du TCCL passent sous le radar s'ils ne sont pas rapportés spontanément par le patient, une mesure qui peut être compliquée, voire non fiable, si ce dernier se retrouve dans un état confusionnel (Powell et al., 2008; Stuart et al., 2012). En plus de cela, les cliniciens posent généralement leur

diagnostic en se fiant au GCS, une mesure qui n'est pas systématiquement recueillie auprès de tous les patients, surtout chez les cas plus légers. Une partie de la solution pourrait se trouver dans une étude réalisée par Albicini et McKinlay (2014) où les chercheurs ont identifié les symptômes les plus caractéristiques et spécifiques des TCCL parmi la constellation de symptômes fréquemment observés à la suite d'un TCCL. Ainsi, les chercheurs de l'étude ont montré que la perte de conscience, le vomissement et l'amnésie antérograde et rétrograde de l'évènement constituent des symptômes cardinaux du TCCL (Albicini & McKinlay, 2014). Ces résultats appuient étroitement les critères cliniques établis par le American Congress of Rehabilitation Medicine (ACRM), soit qu'un diagnostic de TCCL soit posé chez une personne présentant au moins un des symptômes suivant au moment ou dans les instants suivant l'accident : la perte de conscience, l'amnésie post-traumatique antérograde et/ou rétrograde et l'altération de l'état mental (confusion, désorientation, étourdissements) (Albicini & McKinlay, 2014; Carroll et al., 2004). Notons que ces critères demeurent à ce jour les plus couramment acceptés dans la littérature entourant le diagnostic de TCCL (Albicini & McKinlay, 2014; Carroll et al., 2004) et ont donc servi de référence dans la présente thèse notamment dans le cadre de l'étude 1. Par ailleurs, considérant la nature rétrospective de l'étude 1 dont l'objectif était d'effectuer un diagnostic rétrospectif de TCCL, au moins trois des quatre critères diagnostics de l'ARCM devaient être rapportés par le participant pour qu'un TCCL soit diagnostiqué.

Symptômes à court terme post-TCCL

Une panoplie de symptômes somatiques (sommeil, maux de tête, étourdissement, nausées, etc.), cognitifs (difficultés attentionnelles et mnésiques, ralentissement de la vitesse de traitement, etc.) et affectifs (labilité émotionnelle, anxiété, irritabilité, dépression) se manifestent à la suite d'un TCCL (Gioia, Collins, & Isquith, 2008; Prince & Bruhns, 2017; Ruff et al., 2009). La résolution à court terme des symptômes présente une variabilité interindividuelle importante tant aux niveaux de la nature des symptômes que de leur durée. Par exemple, il est attendu que la période de confusion se dissipe dans les premières 24h après l'accident, tandis que les symptômes post-commotionnels de

natures somatique (maux de tête, étourdissement, fatigue), cognitive (attention et mémoire) et affective (irritabilité, dépression) peuvent, quant à eux, prendre jusqu'à trois mois avant de se résorber (Arciniegas, Anderson, Topkoff, & McAllister, 2005).

Symptômes à long terme post-TCCL

Bien que la majorité des individus ayant subi un TCCL se rétablissent de leur accident sans séquelles cliniquement significatives (Levin & Diaz-Arrastia, 2015), environ 10% à 15% des individus souffrent de symptômes au-delà de la période de récupération attendue, soit plus de trois mois post-accident (Iverson, 2005). Ce phénomène est connu sous le nom de syndrome post-commotionnel (Williams, Potter, & Ryland, 2010) et est associé à une constellation de symptômes physique (p.ex. : fatigue, maux de tête, étourdissement), cognitif (p.ex. : difficulté de concentration et de mémoire) et émotionnel (p.ex. : irritabilité, anxiété) (Ryan & Warden, 2003). Puisque les méthodes traditionnellement utilisées pour évaluer le rétablissement suite à un TCC s'intéressent principalement au taux de mortalité et à la dépendance fonctionnelle, celles-ci sont peu adaptées à la réalité du TCCL, considérant la subtilité des atteintes cognitives et comportementales de cette condition (Levin & Diaz-Arrastia, 2015). Ainsi, une des variables davantage adaptées et fréquemment étudiées s'avère le retour au travail ou aux études. En effet, cette mesure représente un bon indicateur du rétablissement d'une personne, à savoir si cette dernière est apte à vaquer normalement à ses activités quotidiennes. Selon une étude publiée par Boake et collègues (2004), les patients prennent fréquemment plus d'un mois avant de retourner au travail et plus de 30% des patients ne peuvent y retourner trois mois après l'accident. Selon une revue systématique sur le sujet, seuls 5% des individus TCCL ne sont pas retournés au travail 12 mois post-accident (Cancelliere et al., 2014). Des facteurs tels qu'avoir plus de 11 années de scolarité, l'absence de nausée/vomissement au moment de l'admission au DU, l'absence de blessures extracraniennes et l'absence de douleur d'intensité sévère (au niveau de : tête, cou, bras/épaule, abdomen/dos, jambes/bassin), ont été associés à un retour au travail plus rapide (Stulemeijer, van der Werf, Borm, & Vos, 2008). Il arrive également que, dans certains cas, des accommodements à

l'environnement de travail soient nécessaires, car certains patients TCCL retournant au travail, rapportent se fatiguer plus rapidement et devoir déployer plus d'efforts pour compléter leurs tâches.

Douleur

La douleur serait plus proéminente chez les TCCL comparativement aux TCC modéré/sévère et se manifesterait généralement sous forme de maux de tête, surtout en phase aiguë (Nampiaparampil, 2008; Nordhaug et al., 2019). En effet, environ 50% à 75% des sujets TCCL rapportent ressentir de la douleur suite à l'accident, et celle-ci se chroniciserait dans 15% des cas (Lavigne, Khoury, Chauny, & Desautels, 2015; Nampiaparampil, 2008). En phase chronique, les maux de tête demeurent la plainte principale, mais la douleur tend à devenir diffuse et peut être ressentie au niveau du cou, du dos et même parfois au niveau des jambes et des pieds (King, Beehler, & Wade, 2015; Lucas, 2015). Plusieurs facteurs ont été identifiés associés à un risque accru de chronicisation de la douleur. Par exemple, un niveau élevé de douleur initiale augmente jusqu'à six fois le risque de chroniciser les symptômes de douleur (Mehta, MacDermid, Richardson, MacIntyre, & Grewal, 2015). D'autres facteurs, tels être un jeune adulte et/ou présenter des symptômes d'anxiété et de dépression suite à l'accident, sont également fortement corrélés au risque de chronicisation de la douleur post-TCCL (Lavigne et al., 2015).

Bien que rares, certaines études se sont penchées sur les mécanismes pathophysiologiques sous-tendant le développement et le maintien de la douleur chronique post-TCCL. Les mécanismes impliqués dans la chronicisation de la douleur chez les TCCL seraient similaires à ceux identifiés dans d'autres conditions générant de la douleur, dont les TO (Grandhi, Tavakoli, Ortega, & Simmonds, 2017). En effet, un débalancement entre les mécanismes inhibiteurs GABAergiques et excitateurs glutaminergiques serait en partie responsable de la chronicisation de la douleur post-TCCL (Irvine & Clark, 2018). Ainsi, les neurones du système nocicepteur atteignent un état d'hyperexcitabilité qui prend de l'expansion dans le SNC à un point tel que les mécanismes

inhibiteurs sont mis en marge (Defrin, Riabinin, Feingold, Schreiber, & Pick, 2015; Zeilig, Enosh, Rubin-Asher, Lehr, & Defrin, 2012). La diffusion de la douleur au-delà du site initial (la tête) s'expliquerait par le fait que le SNC est atteint dans sa globalité, donnant accès à d'autres parties du corps via la communication avec le système nerveux périphérique. Les mécanismes facilitateurs de douleur deviennent alors ancrés dans le SNC, tandis que les voies endogènes inhibitrices de la douleur sont atténuées (Mustafa et al., 2016). La neuroinflammation joue également un rôle prédominant dans la douleur post-TCC (Loggia et al., 2015). Suite au TCC, il y a une perturbation de la perméabilité de la BHE, facilitant le passage ascendant et descendant des médiateurs inflammatoires et la communication entre le système nerveux central et périphérique (Morganti-Kossmann, Rancan, Otto, Stahel, & Kossmann, 2001). L'activation de microglies ainsi que d'astrocytes découlant du TCC produisent et libèrent des substances cytotoxiques, comme les cytokines pro-inflammatoires, qui, à leur tour, facilitent l'hyperactivité des neurones et le dysfonctionnement synaptique de nombreuses régions cérébrales, dont celles impliquées dans le traitement de la douleur, tels le thalamus, l'hippocampe, l'amygdale, le cortex préfrontal (Kovesdi et al., 2012; Lozano et al., 2015; Lyman, Lloyd, Ji, Vizcaychipi, & Ma, 2014; Singh, Trivedi, Devi, Tripathi, & Khushu, 2016).

TCCL et traumatisme orthopédique

Concomitance entre les TO et les TCCL

À ce jour, la majorité des études qui s'intéressent à la concomitance entre les fractures et les TCC ont été effectuées chez une population souffrant d'un TCC modéré ou sévère, dans un contexte de TO multiples (Gross, Schuepp, Attenberger, Pargger, & Amsler, 2012). En effet, de nombreuses études ont démontré une forte incidence de TCC auprès de patients souffrant de multiples blessures orthopédiques, dont plusieurs (60%) seraient responsables des décès dans ce contexte (Gross et al., 2012). Le phénomène « multitrauma », combinant les TCC et les TO, est très courant dans les accidents à haute vélocité (Gross et al., 2012). Par ailleurs, la littérature est plus limitée en ce qui a trait à

l'incidence des TCCL auprès d'individus souffrant de blessures orthopédiques jugées moins sévères. Une étude publiée par Rubin et collègues (2015) a recruté 12 754 patients impliqués dans un accident de véhicule motorisé (à titre de passager, de piéton ou de cycliste) et souffrant minimalement d'une fracture au membre supérieur. Les résultats révèlent que 76% de ceux-ci souffraient de blessures additionnelles, dont 52% étaient répertoriés au niveau de la tête, du cou ou du visage. Bien que cette étude ne précise pas la nature de la blessure à la tête, elle démontre tout de même que ce type de blessure est fréquent chez les victimes de TO. Dans le même ordre d'idées, une étude récente suggère que 75% des patients se présentant au DU avec une fracture mandibulaire souffrent d'un TCCL concomitant (Sobin, Kopp, Walsh, Kellman, & Harris, 2015), soulevant l'hypothèse d'une correspondance entre le lieu de la blessure par rapport à la tête et le risque de subir un TCCL concomitant. De plus, une étude longitudinale effectuée sur une période de 10 ans et rassemblant plus de 653 386 patients victimes d'un accident de voiture a démontré que les deux types de blessures les plus fréquents étaient le TCCL et les fractures (Pan et al., 2014). Par ailleurs, les résultats de ces études ne permettent pas d'obtenir un profil clair à propos du risque de subir un TCCL en contexte de fracture isolée. Pourtant, il s'agit des deux blessures présentant la plus forte prévalence dans leur catégorie respective, soit les TCC et les blessures orthopédiques.

Similarités des mécanismes d'accident

Les TCCL et les fractures isolées partagent plusieurs mécanismes d'accident (chutes accidentelles, accidents impliquant un véhicule motorisé, accidents survenus dans un contexte sportif). En plus des mécanismes d'accident similaires, la biomécanique de ces deux blessures se recoupe, particulièrement pour les blessures au membre supérieur. Par exemple, la majorité des fractures de la clavicule surviennent à la suite d'une chute impliquant un impact direct, et incidemment un transfert de force cinétique, à l'épaule (Horst et al., 2013). En plus de la proximité anatomique entre l'épaule et la tête, la biomécanique de cette fracture est étroitement liée à celle du TCCL, qui, pour sa part, est souvent le résultat d'un coup direct à la tête (Rabinowitz, Li, & Levin, 2014; Thieme, 2009).

Profil de symptômes en contexte de blessures combinées

Tel qu'abordé précédemment, il existe un recoupement entre certains symptômes des TCCL et des fractures. La douleur fait partie des symptômes clés que partagent ces deux blessures, se manifestant, en phase aiguë, de manière distincte (p.ex. : maux de tête chez les TCCL versus douleur au membre fracturé chez les TO), mais dont la similarité devient plus évidente en contexte chronique. Il a notamment été démontré que les patients souffrant d'une blessure orthopédique combinée à un TCC seraient plus à risque de développer de la douleur chronique (McDonald et al., 2020; Walker, 2004). Ceci est particulièrement alarmant considérant que la douleur est perçue comme le principal obstacle au retour au travail et que celle-ci réduit considérablement la qualité de vie. En effet, plusieurs études ont démontré que les TCC, dont les TCCL, pouvaient augmenter le risque de développer un syndrome douloureux régional complexe (SDRC) (Gellman et al., 1992; Jang & Seo, 2020; Park et al., 2009). Le SDRC est une condition de douleur chronique qui se manifeste à la périphérie (p.ex. : au niveau du coude, poignet, etc.) et pour laquelle les personnes souffrant de fractures sont particulièrement à risque. Les symptômes du SDRC sont la douleur, souvent très incapacitante, ainsi que d'autres types d'atteintes de natures sensorielle et motrice, dont une diminution de l'amplitude de mouvements, de l'allodynie (perception de douleur déclenchée par un stimulus normalement indolore) et de l'hyperalgésie (Guthmiller & Varacallo, 2020). L'accentuation du risque de développer de la douleur chronique s'expliquerait par le chevauchement des mécanismes pathophysiologiques de ces deux blessures, impliquant l'interaction synergique entre le SNC et le système neuroinflammatoire.

En plus de la douleur, d'autres études réalisées auprès de cohortes sévèrement blessées ont montré que le fait de subir un TO conjointement à un TCC augmente le risque de développer certains types de complications, dont l'ossification hétérotopique (Bajwa, Kesavan, & Mohan, 2018; Coelho & Beraldo, 2009; Dizdar et al., 2013). En effet, il existe de nombreuses études humaines et animales qui mettent en lumière un taux d'ossification hétérotopique nettement augmentée en contexte de TCC modéré/sévère

combiné à un TO, comparativement à des sujets (humains et animaux) avec seulement une blessure traumatique (Cipriano, Pill, & Keenan, 2009; Dizdar et al., 2013; Foruria et al., 2014). Le taux d'ossification hétérotopique plus élevé en contexte de blessures combinées (TCC et TO) s'expliquerait, à nouveau, par le chevauchement des mécanismes physiopathologiques communs aux deux blessures, à savoir un dysfonctionnement de la perméabilité de la BHE, une augmentation de la substance P et une libération prolongée de cytokines pro-inflammatoires (Evans et al., 2012; Huang et al., 2018). Ce phénomène démontre que la pathophysiologie du TCC peut avoir un impact périphérique en interférant avec la guérison osseuse d'une blessure survenue à distance de la tête.

Ainsi, la littérature a, jusqu'à présent, accordé beaucoup d'importance à l'incidence et à l'impact au plan fonctionnel de subir un TO jugé davantage sévère (multiples fractures) combiné à un TCC modéré/sévère. Ce biais est bien naturel puisqu'il s'agit de populations à haut risque de séquelles à court et à long termes pouvant mener au décès et que ces blessures nécessitent un déploiement important de ressources. Néanmoins, ces mêmes questions méritent d'être investiguées auprès de personnes qui subissent des blessures de moindre sévérité, comme le fait de subir une fracture isolée et un TCC léger. En effet, il s'agit de deux blessures à très forte incidence. Notamment, les TCCL constituent 81% de l'ensemble des TCC (Dewan et al., 2018). Ainsi, les séquelles respectives et combinées ne peuvent passer sous le silence pour le bien-être de patients qui en sont atteints.

Objectifs

Objectifs globaux de la présente thèse

Cette thèse comprenait deux volets distincts. Le premier volet avait pour objectif principal d'investiguer l'incidence d'un TCCL concomitant à une fracture isolée ainsi que son impact clinique sur la récupération orthopédique. Le deuxième volet avait pour objectif d'investiguer les mécanismes physiologiques en contexte de fracture accompagnée, ou non, de blessures traumatiques, en adoptant une approche clinique et théorique.

Objectifs et hypothèses de la première étude

La première étude avait pour objectif principal d'estimer l'incidence de TCCL à partir d'un dépistage rétrospectif (réalisé de manière systématique et selon les critères de l'ACRM) auprès de la population orthopédique ayant subi une fracture isolée au membre supérieur ou inférieur. L'incidence obtenue était ensuite comparée à celle du DU d'un hôpital tertiaire de soins en traumatologie, récoltée de manière prospective auprès des mêmes patients, afin d'établir la proportion de cas TCCL non dépistés au sein de cette population. Cette étude visait aussi à établir si le risque de subir un TCCL variait selon l'emplacement de la blessure orthopédique concomitante. Nous avons postulé que les TCCL et les fractures isolées surviennent fréquemment en concomitance (mécanismes d'accident similaires). Nous estimons également qu'un nombre considérable de TCCL passera inaperçu au DU auprès de la population étudiée, considérant la subtilité des symptômes de TCCL, dans un contexte où la personne se présente au DU avec une blessure douloureuse et surtout, plus visible, pouvant être confirmée avec un test radiologique ou des mesures objectives. Enfin, nous estimions que l'incidence de TCCL varierait selon la proximité anatomique de la fracture par rapport à la tête.

Objectifs et hypothèses de la deuxième étude

La deuxième étude avait pour objectif d'évaluer les effets d'un TCCL sur le niveau de douleur ressentie chez des patients souffrant d'une fracture isolée. Nous avons émis l'hypothèse que le groupe fracture+TCCL rapporterait un niveau de douleur statistiquement plus élevé que le groupe fracture sans TCCL et ce, même après avoir contrôlé pour divers facteurs modérateurs de la douleur (âge, sexe, sévérité des symptômes post-commotionnels, présence d'un agent payeur).

Objectifs et hypothèses de la troisième étude

La troisième étude avait pour objectif d'évaluer les effets de subir un TCCL concomitant à une fracture isolée sur le délai du retour au travail chez des individus qui occupaient un emploi avant l'accident et démontraient l'intention de le réintégrer suite au rétablissement. Notre hypothèse était que le groupe TCCL+fracture nécessiterait un plus

long délai avant de retourner au travail comparativement au groupe contrôle (fracture sans TCCL).

Objectifs et hypothèses de la quatrième étude

La quatrième étude avait pour objectif de comparer l'incidence d'ossification hétérotopique selon la présence, ou non, d'un TCCL chez une population ayant subi une fracture isolée. Cette étude visait également à investiguer l'association entre la présence d'ossification hétérotopique et le délai nécessaire pour retourner au travail suite à l'accident afin de mesurer les effets de cette complication orthopédique. L'hypothèse de cette étude était que la présence de signes d'ossification hétérotopique à proximité du site de la fracture serait statistiquement plus élevée chez les patients ayant subi une fracture et un TCCL comparativement à la cohorte avec fracture, mais sans TCCL. Nous avions également estimé que la présence d'ossification hétérotopique serait positivement corrélée au délai nécessaire pour retourner au travail.

Objectifs et hypothèses de la cinquième étude

La cinquième étude constitue une revue de la littérature dont le but principal était d'explorer l'utilité clinique de la stimulation magnétique transcranienne répétée comme outil d'intervention pour réduire le risque de chronicisation de la douleur chez des personnes ayant souffert de blessures traumatiques. Cette étude avait également pour but d'émettre une opinion scientifique sur la pertinence de cette technique auprès de la population étudiée.

Objectifs et hypothèses de la sixième étude

La sixième étude visait à mesurer les effets de la douleur aiguë sur les mécanismes d'excitabilité corticale du cortex moteur primaire de patients ayant subi une fracture à un membre supérieur. Plus spécifiquement, cette étude visait à déterminer la façon dont l'intensité de la douleur aiguë ressentie se répercutait sur les mécanismes d'excitabilité corticale du cortex moteur primaire. Notre hypothèse était que la douleur aigue créerait un débalancement au niveau des mécanismes d'excitabilité corticale du cortex moteur

primaire seulement chez les sujets rapportant un niveau de douleur d'intensité modérée à sévère. Nous avons spéculé que le groupe souffrant de douleur estimée légère présenterait des mesures d'excitabilité corticale comparables à celles obtenues chez le groupe contrôle formé de sujets sains.

Chapitre 2 – Méthodologie et résultats

Article 1: Incidence rate of mild traumatic brain injury among patients who have suffered from an isolated limb fracture: Upper limb fracture patients are more at risk

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Abstract

Objectives: This study compares the incidence rate of mild traumatic brain injury (mild TBI) detected at follow-up visits (retrospective diagnosis) in patients suffering from an isolated limb trauma, with the incidence rate held by the hospital records (prospective diagnosis) of the sampled cohort. This study also seeks to determine which types of fractures present with the highest incidence of mild TBI.

Patients and methods: Retrospective assessment of mild TBI among orthopaedic monotrauma patients, randomly selected for participation in an Orthopaedic clinic of a Level I Trauma Hospital. Patients in the remission phase of a limb fracture were recruited between August 2014 and May 2015. No intervention was done (observational study).

Main outcome measurements: Standardized semi-structured interviews were conducted with all patients to retrospectively assess for mild TBI at the time of the fracture. Emergency room related medical records of all patients were carefully analyzed to determine whether a prospective mild TBI diagnosis was made following the accident.

Results: A total of 251 patients were recruited (54% females, Mean age = 49). Study interview revealed a 23.5% incidence rate of mild TBI compared to an incidence rate of 8.8% for prospective diagnosis ($x^2 = 78.47$; $p < 0.0001$). Patients suffering from an upper limb monotrauma (29.6%; n = 42/142) are significantly more at risk of sustaining a mild TBI compared to lower limb fractures (15.6%; n = 17/109) ($x2 = 6.70$; $p = 0.010$). More specifically, patients with a proximal upper limb injury were significantly more at risk of sustaining concomitant mild TBI (40.6%; 26/64) compared to distal upper limb fractures (20.25%; 16/79) ($x^2 = 7.07$; $p = 0.008$).

Conclusions: Results suggest an important concomitance of mild TBI among orthopaedic trauma patients, the majority of which go undetected during acute care. Patients treated for an upper limb fracture are particularly at risk of sustaining concomitant mild TBI.

Introduction

Orthopaedic trauma is the most common type of trauma seen in a hospital setting (Urquhart et al., 2006) and accounts for approximately half of all emergency room (ER) injuries treated annually (Mamaril, Childs, & Sortman, 2007).

Musculoskeletal injuries, independent of severity, usually require patients to seek medical care shortly after the accident. Considering the high rate of annual visits, it becomes extremely important for professionals to rapidly address health issues that pose a risk to patients' long-term prognosis. Priority of treatment is established based on primary concerns (i.e. vital signs status and obvious injuries) and injury characteristics (mechanism and severity of injury), therefore sidelining milder or less apparent injuries (Ferree et al., 2014). For example, in multiple musculoskeletal injuries, fractures considered high-risk, such as a hip fracture, will be treated rapidly compared to fractures considered less urgent, such as a clavicle fracture (Ferree et al., 2014). The vast majority of fractures typically occur as a result of accidental falls or traffic accidents (Court-Brown, Bugler, Clement, Duckworth, & McQueen, 2012) where impact velocity is generally a good predictor of the severity of injury. Interestingly, orthopaedic trauma shares highly similar accident mechanisms to traumatic brain injury (TBI) (Cassidy et al., 2004; Court-Brown et al., 2012; Langlois, Rutland-Brown, & Wald, 2006), the latter being associated with nearly 1.7 million hospital visits annually (Centers for Disease & Prevention, 2011). TBI is the result of biomechanical forces imparted to the head, or indirectly through the neck, resulting in a combination of rapid acceleration and deceleration of the brain within the skull (Blennow, Hardy, & Zetterberg, 2012). TBI is frequent among patients suffering from multiple traumas (Gross, Schuepp, Attenberger, Pargger, & Amsler, 2012) as impact velocity resulting in orthopaedic trauma may well have transmitted sufficient force to the head, either directly or indirectly (Langlois et al., 2006), to generate TBI symptoms. In cases of multiple trauma patients involving moderate or severe TBI, medical procedures will immediately initiate treatments for TBI in an attempt to reduce the likelihood of death and minimize long-term functional repercussions (Maas, Stocchetti, & Bullock, 2008),

particularly so as TBI was found to better predict long-term functional deficits than musculoskeletal injuries (Andruszkow, Probst, Grun, Krettek, & Hildebrand, 2013; Gross et al., 2012). Thus, the treatment for fractures is delayed until patients have reached a stable state.

In contrast, in cases of mild TBI, immediate symptoms are far less apparent, therefore making diagnosis more complex (Ruff et al., 2009). Although several inconsistencies exist in the definition of mild TBI, the diagnostic criteria for mild TBI developed by the American Congress of Rehabilitation Medicine (ACRM) have been widely recognized and are frequently used in hospital settings. In addition to the Glasgow Coma Scale (GCS) score obtained at the time of the injury, focal neurological deficit, and CT scan results, ACRM diagnostic criteria for mild TBI assess the presence and duration of mental function alterations including loss of consciousness, loss of memory for events immediately before or after the accident and alteration of mental state at the time of the accident (Carroll et al., 2004). However, a recent report showed that emergency rooms typically use CT scan and the GCS at admission to the hospital to detect potential neurological complications and determine the severity of TBI (Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012). In mild TBI, however, relying on these two indices of TBI severity may be problematic given the poor sensitivity of the GCS to mild TBI symptoms and that only 10–15% of mild TBI cases have a positive CT scan (McAllister & Ferrell, 2002). Other challenges with mild TBI diagnosis include the patients' failure to report the event, the inability to recognize symptoms, and the belief that everything will return to normal without seeking medical assistance (Buck, 2011; Kashluba, Hanks, Casey, & Millis, 2008). In an emergency room setting, where timely decisions critically influence patient's functional recovery, the assessment of mental function alterations may be overlooked by emergency room clinicians (Powell, Ferraro, Dikmen, Temkin, & Bell, 2008; Stuart, Mandleco, Wilshaw, Beckstrand, & Heaston, 2012). Indeed, these professionals are accustomed to assessing and treating perceived emergency injuries in a timely matter and may pay less attention to patients' subjective, seemingly benign symptoms (Powell et al., 2008; Uhl, Rosenbaum, Czajka, Mulligan, & King, 2013). For that reason, mild TBI often goes undiagnosed (Buck,

2011) and, if left untreated, mild TBI is associated with delayed resorption of associated symptoms (Fleminger, 2008).

Interestingly, functional motor symptoms present in the remission phase of an isolated limb fracture (Manara, Taylor, & Nixon, 2015; Mkandawire, Boot, Braithwaite, & Patterson, 2002) are highly similar to short and long-term motor function alterations after a mild TBI including gait stability, motor execution speed and motor learning (De Beaumont et al., 2009; De Beaumont et al., 2013; Slobounov, Slobounov, Sebastianelli, Cao, & Newell, 2007). Taken together, it appears plausible that undiagnosed mild TBI concomitant to orthopaedic trauma may contribute to delayed recovery of orthopaedic symptoms, at least for those symptoms shared with mild TBI (Fleminger, 2008). Therefore, the primary purpose of the present study is to determine the incidence rate of mild TBI among orthopaedic trauma patients who have suffered from an isolated limb fracture and to what extent retrospective assessment of mild TBI diagnostic criteria concords with emergency room diagnosis. Our sample consisted exclusively of orthopaedic patients with an isolated limb fracture who did not experience health complications in the period following the accident. This precautionary step was taken in order to restrict recall bias in cases requiring more complex medical management and longer hospital stay. Moreover, no stratification for orthopaedic injury severity was performed in this study as we intended for our sample to be as representative of the targeted population of interest as possible. We hypothesized that a high rate of mild TBI goes undiagnosed among patients with an isolated limb fracture. This study also attempts to verify whether anatomical proximity of the fractured bone relative to the head is associated with higher risk of concomitant mild TBI.

Patients and methods

Participants were recruited from the orthopaedic clinic of a Level 1 Trauma Hospital between August 2014 and May 2015. All subjects were randomly selected among patients who visited the hospital for a routine orthopaedic follow-up appointment. Patients were eligible for the study if they had suffered from an isolated limb fracture (i.e., one fractured

bone). Exclusion criteria included: subject age under 18, substance-related intoxication, a GCS below 13 at emergency admission (i.e.; to disqualify any patient presenting with moderate or severe TBI according to the GCS scale), patients who experienced health complications other than mild TBI in the period following the injury, and non-extremity fractures (hip, pelvis, ribs, neck, spinal cord, skull). The study was approved by a local ethics committee and all subjects provided written informed consent prior to participation in the study. A financial compensation (i.e., reimbursement of daily parking fees) was given to all subjects participating in the study. Participants were screened for mild TBI through a standardized semi-structured interview conducted by an experienced graduate neuropsychology trainee specializing in mild TBI diagnosis and management. The mild TBI screening procedure took an average of 30 min. Subjects were first asked to answer general demographic questions (gender, age, date of birth, date of the accident) and information related to the injury (mechanism of accident and type of fracture). A standardized mild TBI history form was then administered to verify ACRM diagnostic criteria for mild TBI and related symptoms both at the time of the accident and over subsequent days. Open-ended questions were used for patients to report detailed information about the accident, which allowed for spontaneous and unbiased description of the accident and possible symptoms. If not mentioned by the patient, the experimenter then validated whether they had experienced any of following symptoms: loss of consciousness (LOC), post-traumatic retrograde and anterograde amnesia, dizziness, weakness, numbness, loss of balance, headaches, drowsiness, nausea, tingling, or blurred vision. Retrospective assessment of mild TBI diagnostic criteria was based on diagnostic criteria developed by the American Congress of Rehabilitation Medicine i.e.; any period of loss of consciousness for up to 30 min; any loss of memory for events immediately before or after the accident for as much as 24 h; any alteration of mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); focal neurological deficit(s) that may or may not be transient; and a GCS score falling between 13 and 15 after 30 min. Other, less specific mild TBI symptoms (sleepiness, balance problems, numbness, tingling, blurred vision, weakness, headaches, etc.) were considered as secondary symptoms as

fractures and acute pain are known to induce similar symptomatology (Uhl et al., 2013) (refer to Table 1 for participants' symptoms self-report). ER-related medical records of all participants were thoroughly reviewed and analyzed to determine if an emergency-room diagnosis of mild TBI was made following the accident.

Tableau 1. – Mild TBI related symptoms experienced by participants following the accident

	Number of subjects with a mild TBI experiencing symptoms (n total with a mild TBI = 59) n (%)	**Number of subjects without a mild TBI experiencing symptoms (n total without a mild TBI = 192) n (%)**
Loss of consciousness	44 (74.5)	3 (1.6)
Confusion	51 (86.4)	20 (10.4)
Post-traumatic retrograde amnesia	32 (54.2)	4 (2.1)
Post-traumatic anterograde amnesia	38 (64.4)	3 (1.6)
Headaches	37 (62.7)	23 (12.0)
Loss of balance	19 (32.2)	15 (7.8)
Convulsion	1 (1.69)	0 (0)
Vomiting	11 (18.6)	7 (3.6)
Dizziness	41 (69.5)	29 (15.1)
Weakness	38 (64.4)	59 (30.7)
Numbness	27 (45.8)	61 (31.7)
Drowsiness	33 (55.9)	51 (26.6)

Nausea	27 (45.8)	32 (16.7)
Tingling	18 (30.5)	54 (28.1)
Blurred vision	14 (23.7)	7 (3.6)

Results

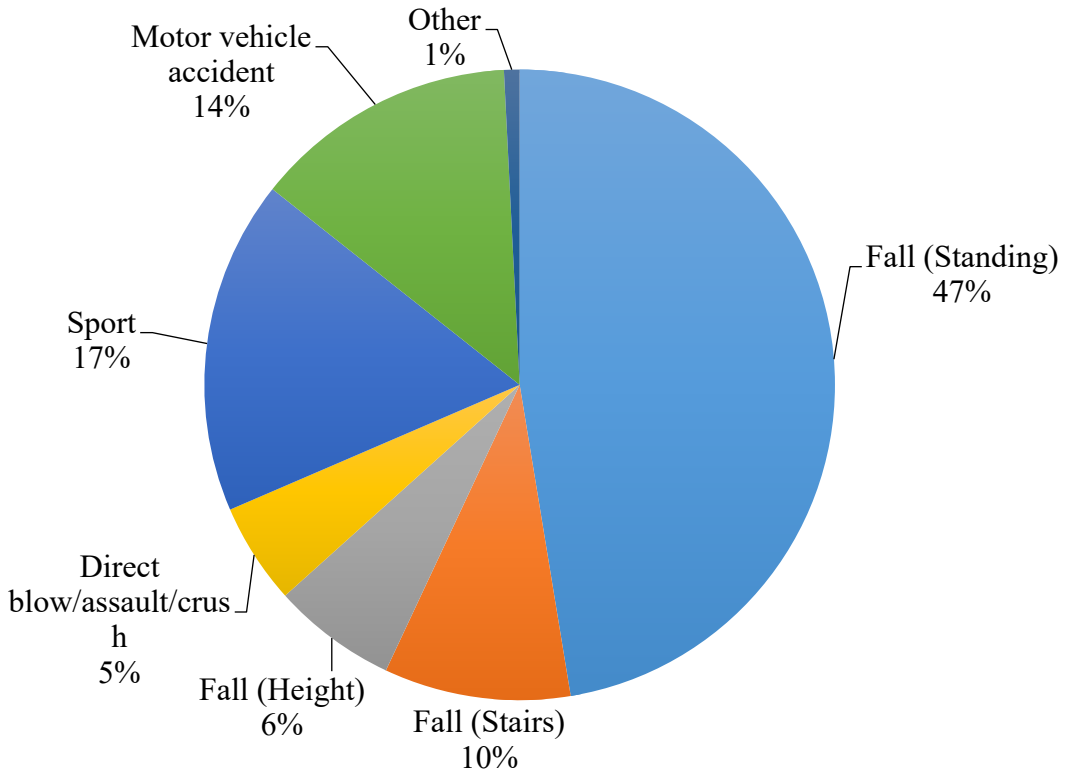
A total of 251 subjects participated in the study, of which 109 (43.4%) suffered from a lower limb fracture (i.e. femur, tibia/ peronei, ankle, foot) and 142 (56.6%) suffered from an upper limb fracture (i.e. clavicle, scapula, humerus, elbow, cubitus, radius, wrist, hand). The mean age was 49 years old (range, 18–86 years old) and 136 were females (54.0%) (Table 2). The most common mechanisms of accident were accidental falls (47.4%; 119/251), sport-related injuries (17.1%; 43/251) and motorized vehicle accidents (13.5%; 34/251) (Fig. 1). On average, participants were interviewed 4.12 (SD = 6.95; range, 1–14 months) months post-injury. A total of 22 participants received a prospective mild TBI diagnosis when assessed at the ER. The median GCS score was 14 (range, 13–15).

Tableau 2. – Descriptive characteristics of study cohort by group

	Total	**Upper Limb Trauma**	**Lower Limb Trauma**	**Mild TBI**	**No TBI**
N (subjects)	251	142	109	59	192
Age (years±SD)	49.0.±15.4	51.5±15.3	45.7±15.4	46.0±16.1	49.9±15.0
Gender (Female [%])	136 (54.0)	82 (57.7)	54 (49.5)	26 (44.1)	110 (57.3)

Time since accident (months±SD)	4.1±7.0	3.1±6.3	5.5±8.1	4.5±6.4	4.0±7.1

Figure 1. – Distribution of the mechanisms of accident in percentages



Incidence rates on concomitant mild TBI diagnosis based on retrospective assessment

The retrospective assessment of mild TBI diagnostic criteria identified a total of 59 mild TBI cases among patients with an isolated limb fracture, which corresponds to an incidence rate of 23.5% (59/251) independently of the type of fracture (i.e.; all types of fractures) (Table 3). Among this sample, 91.5% (54/59) reported experiencing at least 3 out of 4 of the most specific and sensitive ACRM mild TBI symptoms (loss of consciousness, post-traumatic retrograde amnesia, post-traumatic anterograde amnesia, confusion/disorientation).

Furthermore, data from the retrospective assessment of mild TBI showed that patients suffering from an upper limb fracture were at a significantly greater risk of sustaining a concomitant mild TBI when compared to lower limb fracture patients ($x^2 = 6.70$; $p = 0.010$; Fig. 2). Indeed, the former group showed an incidence rate of mild TBI of 29.6% (42/142) whereas the latter group had an incidence rate of 15.6% (17/109). Upper limb fractures were then divided into two distinct groups according to proximity of the fracture to the head: proximal (scapula, clavicle, humerus) and distal (radius, cubitus, wrist, hand). Moreover, Patients with a proximal upper limb injury were significantly more at risk of sustaining a concomitant mild TBI (40.6%; 26/64) compared to distal upper limb fractures (20.3%; 16/79) ($x^2 = 7.07$; $p = 0.008$).

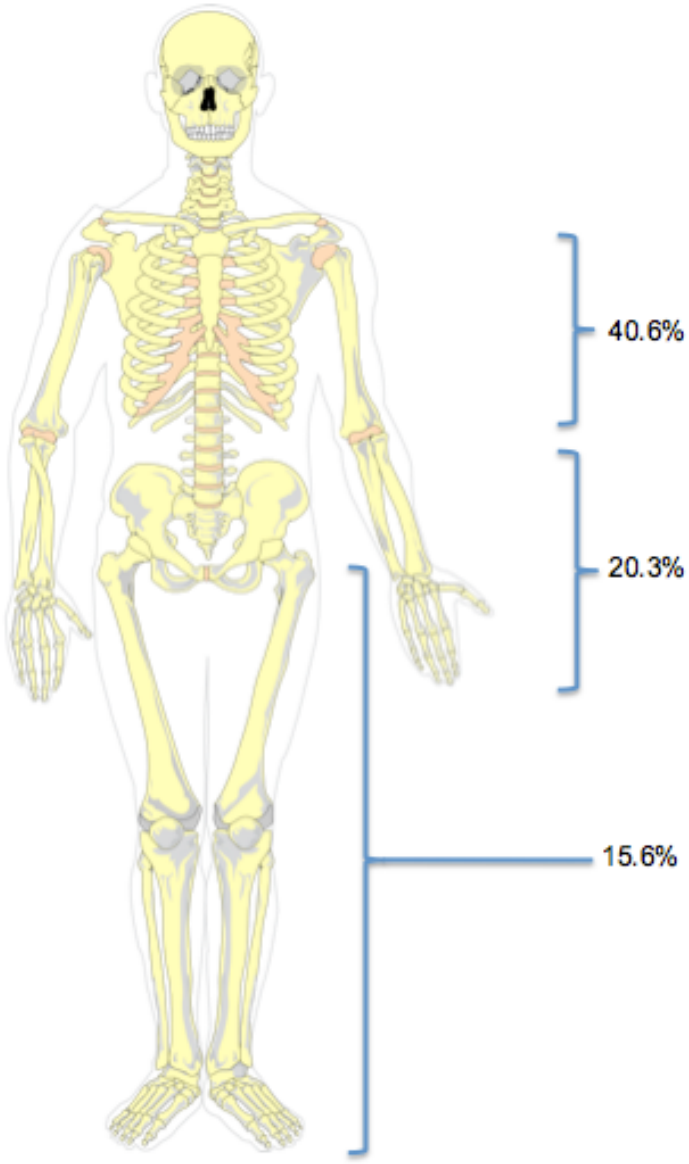
Tableau 3. – Comparison of emergency-room diagnosis and diagnostic data from the retrospective assessment of mild TBI

		Prospective diagnosis	**Retrospective diagnosis**	**Inter-rater reliability on absence of mild TBI**	**Difference between accuracy of diagnosis and agreement on absence of**

					mild TBI (X^2 [p value])
Total limb fractures		8.8 (22/251)	23.5 (59/251)	100 (192/192)	78.5 (p<0.01)*
Upper limb fracture		11.3 (16/142)	29.6 (42/142)	100 (100/100)	42.9 (p<0.01)*
	Proximal	20.3 (13/64)	40.6 (26/64)	100 (38/38)	23.8 (p<0.01)*
	Distal	3.8 (3/78)	20.3 (16/78)	100 (63/63)	12.1 (p<0.01)*
Lower limb fracture		3.7 (4/109)	15.6 (17/109)	100 (92/92)	34.4 (p<0.01)*

Level of significance was set at p<0.05*

Figure 2. – Mild TBI incidence rate among sample based on fracture location



Emergency-room diagnosis versus retrospective assessment of mild TBI

A chi square analysis conducted to determine the level of agreement between Emergency-room diagnosis and diagnostic data derived from the retrospective assessment of mild TBI criteria revealed to be highly significant ($x^2 = 78.47$; $p < 0.0001$). While the level of agreement regarding the absence of mild TBI was perfect (100%; 192/192), common agreement on the presence of mild TBI was considerably lower (37.3%; 22/59). Finally, chi square analyses on the level of agreement for upper limb fractures ($x^2 = 42.93$; $p < 0.001$) and lower limbs fractures ($x^2 = 34.36$; $p < 0.001$) were

highly significant. More specifically, common agreement on the presence of mild TBI was 38% (16/42) for upper limb fracture patients and 35% (6/17) for lower limb fracture patients.

Discussion

The present study aimed to determine the incidence rate of mild TBI among individuals treated for an isolated limb fracture and to compare agreement between emergency room diagnosis and diagnostic data from retrospective assessment of mild TBI. The results of the present study revealed that patients with an isolated limb fracture are particularly at risk of sustaining concomitant mild TBI. More specifically, fractures of the upper limb, especially when anatomically close to the head, present the highest incidence rate of mild TBI. Alarmingly, this study highlights a sharp discrepancy between emergency room diagnosis and diagnosis based on a comprehensive retrospective assessment of mild TBI diagnostic criteria, suggesting that a high rate of mild TBI may go undetected in the emergency room when concomitant to an isolated limb fracture.

Most studies interested in the co-occurrence of musculoskeletal injuries and TBI were concerned with severely injured patients who presented with moderate to severe TBI (Gross et al., 2012). The present study, however, highlights that patients suffering from less severe injuries, such as an isolated limb fracture, are also highly vulnerable to head injuries. This finding is not surprising considering that both types of trauma injuries are caused by the application of similar biomechanical forces in the event of an accident, such as falls, traffic accidents, and sports-related injuries (Cassidy et al., 2004; Langlois et al., 2006).

Another major finding from this study was that the incidence of mild TBI is higher in patients with isolated upper limb fractures. When upper limb fracture data were further stratified to include the notion of the distance from the head, namely proximal (scapula, clavicle, humerus) versus distal (radius, cubitus, wrist, hand) upper limb fractures, we found that patients with a proximal fracture were significantly more at risk to sustain a concomitant mild TBI relative to distal fracture counterparts. This result pattern suggests

that the susceptibility to mild TBI increases as a function of anatomical proximity of the fractured bone relative to the head. This finding is supported by a recent study that showed a 75% incidence rate of mild TBI among a small cohort of individuals who had suffered from an isolated mandible fractures (Sobin, Kopp, Walsh, Kellman, & Harris, 2015).

The most striking result of the current study is the markedly different incidence rates of mild TBI diagnosis among patients with concomitant isolated orthopaedic trauma when comparing emergency room diagnosis as opposed to a comprehensive retrospective assessment of mild TBI based on ACRM diagnostic criteria. Indeed, the retrospective interviews conducted at follow-ups suggested that among orthopaedic trauma patients with concomitant mild TBI symptoms, over 60% of them had not originally been detected in emergency care settings of a Level 1 Trauma Centre Hospital. This is particularly striking considering that over 90% of patients diagnosed with mild TBI based on retrospective interviews reported at least 3 out of 4 ACRM diagnostic criteria for mild TBI. These results are in line with current literature suggesting that mild TBI often goes undiagnosed (Buck, 2011). However, it is important to note that one of the major issues related to undiagnosed mild TBI cases has to do with a majority of patients not seeking medical attention (Setnik & Bazarian, 2007). This is at odds with the current study sample who were all admitted to the emergency room and whose mild TBI symptoms nonetheless went undetected. One plausible explanation for the present study findings is the seemingly benign, typically invisible nature of the mild TBI symptoms as opposed to the often graphic and discomforting manifestations of isolated limb fracture. Accordingly, emergency room clinicians may feel compelled to prioritize treatment of the more overt symptoms at the expense of covert ones, particularly in cases where CT scan results are negative and GCS scores fall within the mild TBI range. The current study findings stress the need for a rigorous, comprehensive emergency room assessment of mild TBI diagnostic criteria that go beyond initial GCS score and CT scan results, particularly so in patients who sustain a proximal upper limb fracture. Indeed, since mild TBI is almost an entirely symptom-based diagnosis, a more thorough screening procedure should include

an accurate history of the accident and a physical and neurological examination. This screening procedure can be conducted through a structured interview assured by a duly trained, emergency-room health professional to verify the presence of the ACRM criteria. Medical practitioners should then be informed of suspected mild TBI cases in order to evaluate the pertinence of mild TBI diagnosis based on a more in-depth analysis of related symptoms. Knowing that early management of mild TBI cases considerably improves mild TBI recovery time and the persistence of symptoms (Marshall et al., 2012), thereby reducing direct as well as indirect costs linked to prolonged disability, a more careful assessment of mild TBI symptoms in orthopaedic trauma patients, particularly those with a upper limb fracture, is warranted. Finally, and as expected, emergency room and retrospective assessment of mild TBI revealed a perfect agreement on non-TBI orthopaedic trauma patients.

The main limitation to this study is having to rely on retrospective self-reports of mild TBI symptoms which might cause a recall bias considering the delay between the trauma and the assessment. Optimal assessment of ER diagnostic accuracy would be achieved by having an independent expert rater prospectively evaluating mild TBI patients upon ER admission. Also, study sample revealed a higher than expected rate of females (54%) compared to the emergency room hospital records (41%). Although this over representation of females among our study sample could have introduced a slight bias in the current study findings, this possibility appears quite unlikely considering that females were less represented among mild TBI victims than male counterparts (refer to Table 1 for complete statistics on gender differences). In addition, results should be interpreted with caution considering that data collection took place in a single Level I Trauma Center Hospital, which restricts generalization of the current study findings to other hospital settings. The present findings do, however, stress the need to conduct a multi-centric study on the association between isolated orthopaedic trauma and concomitant mild TBI. Interestingly, recruitment was carried out over a 10-month period allowing the sample to be highly representative of the various types of seasonal injuries. Finally, future longitudinal studies are needed to better characterize recovery patterns among

orthopaedic trauma patients with mild TBI and how they differ from those of orthopaedic trauma patients with no head injury.

Conclusions

In conclusion, these findings may bear major clinical significance as optimal mild TBI recovery is highly dependent on early diagnosis and adequate management of acute symptoms (Levin & Diaz-Arrastia, 2015). Indeed, early detection could potentially reduce likelihood of developing persistent functional disability associated with mild TBI symptoms (physical, cognitive, emotional, behavioral), thereby improving both the quality of life and the likelihood of reintegrating daily activities such as work and school (Marshall et al., 2012). The implementation of an ER-based systematic and standardized screening procedure for mild TBI among orthopaedic trauma patients, regardless of injury severity, may greatly improve diagnosis accuracy. Such systematic TBI screening procedures may prove to be of great clinical utility, particularly for orthopaedic patients with proximal upper limb fractures who were shown to exhibit the highest rates of concomitant mild TBI diagnosis when assessed retrospectively.

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Article 2: Comorbid mild traumatic brain injury increases pain symptoms in patients suffering from an isolated limb fracture

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Abstract

Objectives: This study seeks to evaluate the effects of a mild traumatic brain injury (mTBI) on pain in patients with an isolated limb fracture (ILF) when compared to a matched cohort group with no mTBI (control group).

Patients and methods: All subjects included in this observational study suffered from an ILF. Groups were matched according to the type of injury, sex, age, and time since the accident. Main outcome measurements were: Standardized semi-structured interviews at follow-up of a Level I Trauma Center, and a questionnaire on fracture-related pain symptoms. Factors susceptible to influence the perception of pain, such as age, sex, severity of post-concussive symptoms, and worker compensation were also assessed.

Results: A total of 68 subjects (36 females; 45 years old) with an ILF were selected, 34 with a comorbid mTBI and 34 without (24/34 with an upper limb fracture per group, 71% of total sample). Patients with mTBI and an ILF reported significantly higher pain scores at the time of assessment (mean: 49 days, SD: 34.9), compared to the control group ($p < 0.0001$; mean difference 2.8, 95% confidence interval 1.8–4.0). Correlational analyses show no significant association between the level of pain and factors such as age, sex, severity of post-concussive symptoms, and worker compensation.

Conclusions: Results suggest that mTBI exacerbate perception of pain in the acute phase when occurring with an ILF, and were not explained by age, sex, post-concussive symptoms, or worker compensation. Rather, it appears possible that neurological sequelae induced by mTBI may interfere with the normal recovery of pain following trauma.

Introduction

According to recent estimates, nearly 30 million individuals suffer from orthopaedic trauma in the United States each year (Centers for Disease, 2011). Orthopedic trauma is defined as an injury to the musculoskeletal system, such as bones, joints, or ligaments (Pollak & Watkins-Castillo, 2013). Among them, fracture is the most common type of injury and typically leads to emergency room visits (Ootes, Lambers, & Ring, 2012). Acute severe pain is considered a natural response to a bone fracture and is experienced by 70 to 100% of trauma patients (Albrecht et al., 2013; Archer, Castillo, Wegener, Abraham, & Obremskey, 2012; Platts-Mills et al., 2016). According to the International Association for the Study of Pain (IASP), resolution of acute pain typically aligns with tissue and bone healing, which usually happens within three months following the accident (Vijayan, 2011). Of note, acute pain is defined as "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness" (Carr & Goudas, 1999). Despite being an integral part of recovery, pain is known to negatively affect quality of life and interfere with return to work (Albrecht et al., 2013). For instance, for a fracture as mild as a distal radius fracture, studies show that more than 75% of patients report at least minimal pain and disability associated to this pain more than 6 months after the injury (MacDermid, Roth, & Richards, 2003). Despite early treatment, such as surgical procedure and/or pharmacological treatment, a fair portion of this population carries pain symptoms beyond the expected recovery period, therefore becoming both an important personal and financial burden. Furthermore, acute pain is an important marker of pain chronification such that excessive pain levels in the first weeks of injury can predict transition from acute to chronic pain (Mehta, MacDermid, Richardson, MacIntyre, & Grewal, 2015; Moseley et al., 2014; Pergolizzi, Raffa, & Taylor, 2014). Interestingly, mild traumatic brain injury (mTBI) is frequent among patients with an isolated limb fracture (ILF) (24%) and is also known to induce pain such as headaches but also widespread body pain (Jodoin et al., 2016; Lahz & Bryant, 1996; Lavigne, Khoury, Chauny, & Desautels, 2015; Nampiaparampil, 2008). For example, a recent study showed that mTBI can induce bodily pain during the chronic phase (more than 6 months post-

injury) in more than 64% of patients with an mTBI (Mollayeva, Cassidy, Shapiro, Mollayeva, & Colantonio, 2017). Despite that, most studies interested in the relationship between pain and mTBI have looked at the effects of pain on post-mTBI symptoms (Iverson & McCracken, 1997; Smith-Seemiller, Fow, Kant, & Franzen, 2003). Indeed, it is shown that pain can induce similar cognitive symptoms as those observed following mTBI (Smith-Seemiller et al., 2003). However, to our knowledge, very few studies, if any, have looked at the effects of comorbid mTBI on acute pain in ILF patients other than headaches within three months of the injury. The scarcity of knowledge on acute pain after mTBI is particularly problematic in polytrauma patients in whom pain represents one of the main obstacles preventing them from resuming an active lifestyle. Indeed, it is possible that bodily pain induced by mTBI exacerbates acute pain after an ILF by interfering with functional recovery. Therefore, we hypothesized that patients with an ILF suffering from a comorbid mTBI will report higher levels of fracture-related pain at the time of the assessment when compared to a matched ILF cohort without a mTBI.

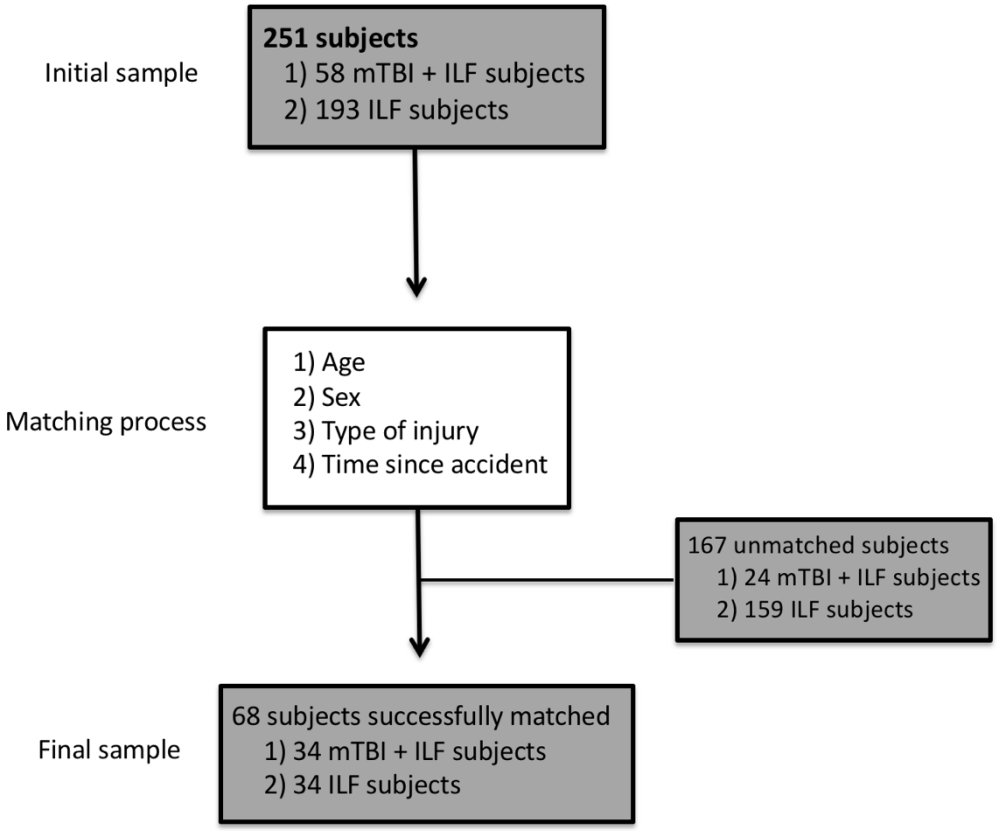
Methods

Case control subjects selection

Subjects were selected from a previous sample, which consisted of 251 subjects with an ILF (58 subjects with an ILF + mTBI and 193 subjects with an ILF only) from a study conducted by our group and seeking to evaluate the incidence rate of mTBI among an ILF population (For more details Jodoin et al., 2016). To compare both groups, we proceeded by using a one-on-one matching approach based on the following criteria: 1) age ($\pm$5 years); 2) sex; 3) type of injury (fractured bone); 4) time elapsed since accident ($\pm$30 days). A match was made if they had suffered from injuries within the same category, namely proximal upper limb fracture (clavicle, scapula, humerus), distal upper limb fracture (elbow, cubitus, radius, wrist, hand), leg fracture (femur, tibia/peronei), and foot/ankle fracture. The matching process focused primarily on pairing subjects within injury categories, in most cases the same fractured bone. This was done in order to limit possible confounding factors known to affect injury severity, thereby facilitating study

interpretation. This matching process led to the formation of 34 identical pairs (See participant flowchart in Fig. 1). The remaining subjects who could not be matched according to abovementioned criteria or who were seen at the orthopaedic clinic more than 3 months post-accident (24 with a mTBI and 159 without a mTBI) were excluded from the present study (Jodoin et al., 2016). This study followed the clinical criteria (loss of consciousness, loss of memory for events immediately before or after the accident and alteration of mental state at the time of the accident) for mTBI established by the American Congress of Rehabilitation Medicine (ACRM), to diagnose all 58 patients with a mTBI (Jodoin et al., 2016). Patients received a diagnosis of mTBI if they presented at least three out of the four ACRM criteria. All patients were screened for mTBI through a semi-structured interview following a standardized procedure for mTBI diagnosis. Open-ended questions were used for patients to report detailed information about the accident, which allowed for spontaneous and unbiased description of the accident and possible symptoms. If not mentioned by the patient, the experimenter then validated whether they had experienced any of the following symptoms previously mentioned. All participants included in the study suffered from an ILF and were 18 years or older. The Rivermead Post Concussion Symptoms Questionnaire was administered at follow-up to assess the severity of symptoms typically observed following a traumatic brain injury such as headaches, sleep disturbances, fatigue, and blurred vision (King, Crawford, Wenden, Moss, & Wade, 1995). Participants were excluded if they presented any of the following characteristics: a Glasgow Coma Scale (GCS) below 13 at emergency admission, substance-related intoxication, health complications unrelated to mTBI in the period following the injury, and non-extremity fractures (hip, pelvis, ribs, neck, spinal cord, skull). Furthermore, participants with an associated peripheral nerve injury, a chronic regional pain syndrome, an infection, a fracture nonunion, or malunion were also excluded.

Figure 1. – Participant flowchart



Patient evaluation

A pain related questionnaire routinely used by the orthopaedic trauma team was administered during the follow-up assessment at the orthopaedic clinic of a level I Trauma Center (see index to consult the pain questionnaire). During an individual semi-structured interview conducted within three months post-injury, subjects were verbally asked to rate different fracture-related pain symptoms on a 0-to-10 likert scale, where 0 corresponded to no pain and 10 referred to excruciating pain. For example, subjects had to rate the maximum and minimum level of pain since the accident (see Table 3). Subjects were also asked to rate, on a scale from 0-to-10, the level of pain at the time of the assessment.

Statistics

Descriptive analyses were used to characterize and compare the two groups from our study (ILF subjects with a mTBI and ILF subjects without a mTBI). Results from descriptive analyses are expressed as means, SD (standard deviation), medians, and percentages (refer to Table 1). We then conducted paired samples t-test analyses, to assess reported pain levels across groups. Mean differences and confidence intervals set at 95% were also provided. Correlational analyses were conducted to evaluate the effects of age, sex, post-concussive symptoms, and workers' compensation status, on the perception of pain. Statistical tests were carried out with a a-level fixed at 0.05. The Bonferroni correction approach was used to control for multiple comparisons. Statistical analyses were performed using IBM SPSS Statistics software version 24 (Armonk, NY, United States).

Results

A total of 68 subjects were selected, from a study cohort of 251 individuals recruited by our group. This sample consisted of 34 subjects (18 females; mean = 45 years old; median = 47.5) who suffered from a mTBI with an ILF (ILF + mTBI), and 34 matched subjects (18 females; mean = 45 years old; median = 47.5) who suffered from an ILF with no mTBI (ILF) (see Tables 1 and 2). On average, participants were interviewed 49.0 days (SD = 34.9; median = 39.5; range, 5–120 days) post-injury. As hypothesized, relative to ILF patients,

the ILF + mTBI group reported significantly higher levels of persistent pain at the time of assessment ($p < 0.0001$; mean difference 2.8, 95% confidence interval 1.8–4.0) after Bonferroni correction for multiple comparisons, suggesting that comorbid mTBI significantly augments persistent pain in the event of an ILF. After Bonferroni correction, the ILF + mTBI group reported significantly higher levels of maximum ($p = 0.005$; mean difference 2.4, 95% confidence interval 0.8–4.1) and minimum ($p < 0.0001$; mean difference 2.0, 95% confidence interval 1.0–2.9) pain, when compared to the ILF group (see Table 3). Additional correlational analyses were conducted to measure the effects of age and sex on pain level at the time of assessment. Results show no significant association between the level of pain and age at the time of recruitment ($r = 0.15$, $p = 0.39$). Similarly, sex was unrelated to the pain level reported at the time of assessment ($r = 0.03$, $p = 0.85$). Correlational analyses on measures collected at the time of assessment were conducted to probe the potential association between the severity of reported post-concussive symptoms and pain levels. None of the post-concussive symptoms except for daytime sleepiness correlated with pain levels ($r = 0.35$, $p = 0.04$), but the latter was negatively correlated with pain. Again, none of the Pearson correlation was found to be significant. Finally, among the ILF + mTBI group, potential secondary gains from workers' compensation plan were unrelated to the reported level of pain at the time of the assessment ($r = 0.09$, $p = 0.77$).

Tableau 1. – Descriptive characteristics of study cohort by group

	Total	**mTBI**	**No TBI**
N (subjects)	68	34	34
Age **Average years (SD)** **Median**	 45.6 (14.6) 47.5	 45.5 (14.8) 47.5	 45.8 (14.5) 47.5
Sex **(Female [%])**	 36 (53)	 18 (53)	 18 (53)
Time since accident **Average days (SD)** **Median** **Range**	 49.0 (34.9) 39.5 [5 – 120]	 50.2 (37.5) 40.0 [5 – 120]	 47.8 (32.7) 36.5 [8 – 120]

Tableau 2. – Type of injury

	Total	**mTBI**	**No TBI**
Upper limb fracture (%)	48 (71)	24 (71)	24 (71)
Distal upper limb fracture (elbow, cubitus, radius, wrist, hand) (*number of patients*)	22	11	11
Proximal upper limb fracture (clavicle, scapula, humerus) (*number of patients*)	26	13	13
Leg fracture (femur, tibia/peronei) (*number of patients*)	8	4	4
Foot/ankle fracture (*number of patients*)	12	6	6

Tableau 3. – Self-perception of pain by group

	mTBI	No TBI	Mean difference (95% confidence interval)	t	P-value
Current pain			2.8 (1.8 – 4.0)		
Mean (SD)	3.7 (2.7)	0.9 (1.2)		5.3	<0.0001*
Median	4.0	0			
Maximum pain			2.4 (0.8 – 4.1)		
Mean (SD)	5.8 (3.2)	3.4 (2.6)		3.0	0.005*
Median	7.0	3.0			
Minimum pain			2.0 (1.0 – 2.9)		<0.0001*
Mean (SD)	2.6 (2.5)	0.6 (1.1)		4.2	
Median	2.5	0			

Level of significance was set at $p<0.05$*

Discussion

This study provided new insights on acute pain levels of patients who suffered from an ILF, with or without a comorbid mTBI. The results of the present study revealed that patients with an ILF, and a comorbid mTBI, report significantly higher levels of pain when measured in the first three months after the accident. Given that pain is the most common and most debilitating symptom after orthopaedic trauma (Platts-Mills et al., 2016), the current findings suggest that mTBI possibly interferes with recovery from an orthopaedic trauma. Moreover, this study could not reveal any association between pain perception in the post-acute phase and orthopaedic trauma prognostic factors such as age, sex and mTBI symptoms severity. Most studies on mTBI, when interested in pain, have focused on outcomes such as headaches. The present study extends previous studies in highlighting that mTBI can exacerbate the perception of bodily pain induced by another trauma injury during the acute phase. This provides a new insight on the potential

role of comorbid mTBI on functional recovery in ILF patients. It has been suggested that persistent pain in mTBI may be explained, at least partially, by a concept called pain catastrophizing (Chaput, Lajoie, Naismith, & Lavigne, 2016). Pain catastrophizing is defined as a tendency to exaggerate pain perception and to ruminate more than the average person in a context of pain (Quartana, Campbell, & Edwards, 2009). Chaput and colleagues found that patients who report more mTBI symptoms are also more likely to exaggerate pain description. In the current study, however, pain catastrophizing in ILF patients who sustained a comorbid mTBI did not appear to contribute to the present study findings as post-hoc correlational analyses showed that post-concussive symptoms self-reports were unrelated to reported pain symptoms. Although conjectural, multiple factors may contribute to pain amplification observed in the mTBI + ILF group. Among them, a recent study conducted in polytrauma rodents involving a TBI and a fractured bone showed an increase in neuroinflammation, an injury mechanism shared by both injuries and that is centrally involved in the transition from acute to chronic pain (Shultz et al., 2015). Other factors such as an alteration in neuroplasticity, defined as the brain's capacity to modify and reorganize itself, occurs in both injuries and is associated with prolonged symptoms (De Beaumont, Tremblay, Poirier, Lassonde, & Theoret, 2012; May, 2008). Although speculative, future studies should assess the potential contribution of lesioned pain matrix structures after mTBI in disrupting the normal course of pain recovery after a musculoskeletal injury. Moreover, the clinical significance of these study findings is highlighted when considering the high incidence rate (nearly 24% of all cases of ILF) of mTBI among patients who have suffered from an ILF, especially since pain is considered the most debilitating symptom following a trauma (Jodoin et al., 2016; Mehta et al., 2015). Indeed, pain is a strong predictor of long-term functional disability, if not treated rapidly, leading to increased health care expenditures, and loss of productivity (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Mehta et al., 2015). Furthermore, pain in mTBI is also associated with a longer recovery, known to exacerbate cognitive and emotional symptoms (Weyer Jamora, Schroeder, & Ruff, 2013). Interestingly, data from this study showed that reported pain levels at the time of the assessment were unrelated

to access to workers' compensation plans with mTBI victims. Therefore, persistent pain in patients with mTBI cannot be explained by the potential incentives associated with secondary gains. The main limitation of this study is the absence of a pain-related medication registry. However, given the matched-control study design controlling for type and location of injury, delay since injury, age and sex, it appears unlikely that pain-related medication significantly differed across groups to compromise the validity of our study findings. Accordingly, future studies should take into consideration pain-related medication, from the time of the injury to the evaluation date, to control for potential medication-related bias. Moreover, future studies should longitudinally follow patients over time, from the emergency room visit up to one year after the accident, to evaluate the effects of mTBI on pain from the acute to the chronic injury phases. Psychological adjustment characteristics, such as depression and anxiety, should also be taken into consideration given that it can affect the perception of pain following an orthopaedic trauma (Vranceanu et al., 2014).

Conclusions

In conclusion, our findings highlight that mTBI exacerbates pain perception early on (acute phase), when occurring in concomitance with an ILF. From a clinical standpoint, these preliminary results are important considering the high incidence of both injuries. Furthermore, this study furthers our understanding of pain following trauma, the latter being the primary reason for individuals to seek medical assistance (Platts-Mills et al., 2016). In the current study sample, prognostic factors such as age, sex, post-concussive symptoms and workers compensation did not influence pain perception. The moderating effects of mTBI on pain recovery warrant further attention in order to identify strategies for preventing pain from becoming chronic and enhancing recovery.

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Article 3: Effects of concomitant mild traumatic brain injury on resuming work after suffering from an isolated limb fracture: A cohort study

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Abstract

Background: The objective is to explore the effects of concomitant mild traumatic brain injury (mTBI) on return to work (RTW), among patients suffering from an isolated limb fracture. This follow-up study included a total of 170 working age subjects with an isolated limb fracture and was conducted in a phone interview approximately 1-year post trauma. 41 had experienced an mTBI and 129 did not.

Methods: Data were obtained through a phone interview conducted on average 20.7 months (SD = 9.6 months) post-accident. The main outcome measure was the number of days taken to RTW after the injury. Demographic information was also gathered during the phone interview. Workers' compensation status was obtained through the hospitals' orthopaedic clinic data.

Results: The mTBI group took on average 329.7 days (SD = 298.0) to RTW after the injury, as opposed to 150.3 days (SD = 171.3) for the control group ($p < 0.001$). After excluding patients who received workers' compensation, the mTBI group still missed significantly more days of work (M = 299.4 days; SD = 333.0) than the control group (M =105.2 days; SD = 121.6) ($p < 0.0001$).

Conclusion: This study shows that mTBI increases work disability by preventing working-age individuals from rapidly returning to work.

Introduction

Orthopaedic trauma is highly prevalent and is the leading cause of work disability (Bergen, Chen, Warner, & Fingerhut, 2008; Ezzati et al., 2002; Urquhart et al., 2006). There are various types of orthopaedic trauma, with fractures being the most common (Claes, Recknagel, & Ignatius, 2012; Ootes, Lambers, & Ring, 2012). Outcomes following such injury vary greatly according to a number of factors such as type (fractured bone) and severity of injury, demographic factors (gender, age, income), and premorbid conditions (MacIntyre & Dewan, 2016; Murgatroyd, Harris, Tran, Cameron, & Murgatroyd, 2016; Sluys, Shults, & Richmond, 2016). Return to work (RTW) is considered an important outcome measure of functional recovery following injury as it indicates that working-age patients are healthy enough to return to prior occupations (Clay, Newstead, & McClure, 2010; Ownsworth & McKenna, 2004; Waljas et al., 2014). Delayed RTW is associated with poorer physical, psychological, and social health as well as productivity loss (de Putter et al., 2012; Saltychev, Eskola, Tenovuo, & Laimi, 2013; Shi, Sinden, MacDermid, Walton, & Grewal, 2014; Williamson et al., 2009). Productivity cost, defined as the cost associated with production loss due to inability to work after an injury, an illness or a premature mortality, represents a major financial burden for both the individual and the society (de Putter et al., 2012; Pynsent, Faibank, & Carr, 2004).

It was shown that various factors, such as concomitant injuries, might impact recovery and therefore delay RTW (Borgna, Klein, Harvey, & Batstone, 2013). Mild traumatic brain injury (mTBI) is common among patients suffering from an isolated limb trauma, with an incidence rate estimated at 23% (Jodoin et al., 2016). Interestingly, mTBI is known to delay RTW. It has been suggested that patients who have sustained an mTBI with no additional injuries, usually RTW within 3– 6 months, although they may still report symptoms (Cancelliere et al., 2014; Vikane et al., 2016). Furthermore, it has been shown that mTBI significantly exacerbates post-acute pain in an orthopaedic cohort who suffered an isolated fracture (Jodoin et al., 2017). Considering that pain is a major factor delaying RTW and that mTBI can interfere with orthopaedic recovery (Fort et al., 2011; Jodoin et al.,

2017), it appears plausible that mTBI is a putative risk factor of unfavourable prognosis after an isolated limb fracture which may contribute to work absenteeism in this population. Despite the frequent co-occurrence of these injuries, no study has precisely looked at the potential contributing effect of mTBI on RTW among individuals who have suffered from an isolated limb trauma. The purpose of the study is to compare the overall delay before RTW among patients who have suffered from an mTBI concomitant to an isolated limb fracture to the delay found in an orthopaedic cohort without an mTBI. Therefore, we hypothesized that the presence of a concomitant mTBI in this population will increase the delay taken to RTW.

Methods

Subjects were recruited among participants from a previous study conducted by our group at the orthopaedic clinic of a Level 1 Trauma Hospital seeking to determine the incidence rate of mTBI among patients with an isolated limb fracture (for more details: (Jodoin et al., 2016). A total of 252 patients with an isolated limb trauma participated in this study, of which 58 had suffered from a concomitant mTBI based on the American Congress of Rehabilitation Medicine (ACRM) clinical criteria (loss of consciousness, loss of memory for the events immediately before or after the accident an alteration of mental state at the time of the accident) (Carroll, Cassidy, Holm, et al., 2004). Patients were screened for the presence of mTBIs through a standardized semi-structured interview allowing to collect self-reported mTBI-related symptoms. Patients' medical files were also screened to gather information related to the accident and therefore also contributed to establishing mTBI diagnoses. A diagnosis of mTBI was given if patients reported having at least three out of the four ACRM criteria. All subjects included in this study suffered from an isolated limb fracture and were 18 years or older. The study was approved by a local ethics committee, and all subjects provided written informed consent prior to participation in the study. Participants were excluded if they presented any of the following characteristics: a Glasgow Coma Scale (GSC) below 13 at emergency admission, substance-related intoxication, health complications unrelated to mTBI in the period

following the injury, and non-extremity fractures (hip, pelvis, ribs, neck, spinal cord, and skull). Furthermore, participants with an associated peripheral nerve injury, a chronic regional pain syndrome, an infection, a non-union or malunion were excluded. Lastly, subjects who had retired or were unemployed at the time of the phone interview were excluded from the present study, since RTW is the primary outcome of this study.

During the phone interview, subjects were asked the specific date at which they returned to work following the accident. The time taken before returning to vocational activities was obtained by calculating the number of days elapsed between the day of the accident and the first day back to work. For subjects who had not returned to work following the accident, a value was assigned by calculating the number of days between the date of the accident and the date of the phone interview. Although this approach underestimates the number of days necessary for these patients to return to work, days off work in patients with incomplete recovery were included in the analyses as it provides valuable information on RTW among this population (Reynolds, Paniak, Toller-Lobe, & Nagy, 2003). For demographic purposes, subjects were also asked to report an estimation of their annual income using the official income scale from the Quebec' s Ministry of Finance (Québec, 2013). Finally, considering the well-documented effects of workers' compensation on RTW (Bouchard, Garret, Favard, Charles, & Ollat, 2014; Bush et al., 2005; Hou, Tsauo, Lin, Liang, & Du, 2008; Morris et al., 2015; Shields, Thirukumaran, Thorsness, Noyes, & Voloshin, 2016), compensation status was obtained through the hospital's orthopaedic clinic database. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies to report our study.

Statistics

Descriptive analyses were used to characterize the two groups from our study cohort (subjects with an mTBI and subjects without an mTBI) and are expressed in means, SD (standard deviation), and percentages. The mTBI group and non-mTBI group were compared using chi-square test for categorical variables and t-test for continuous

variables. Variations among subjects in delays between the date of the accident and the date of the phone interview were controlled for in the statistical model.

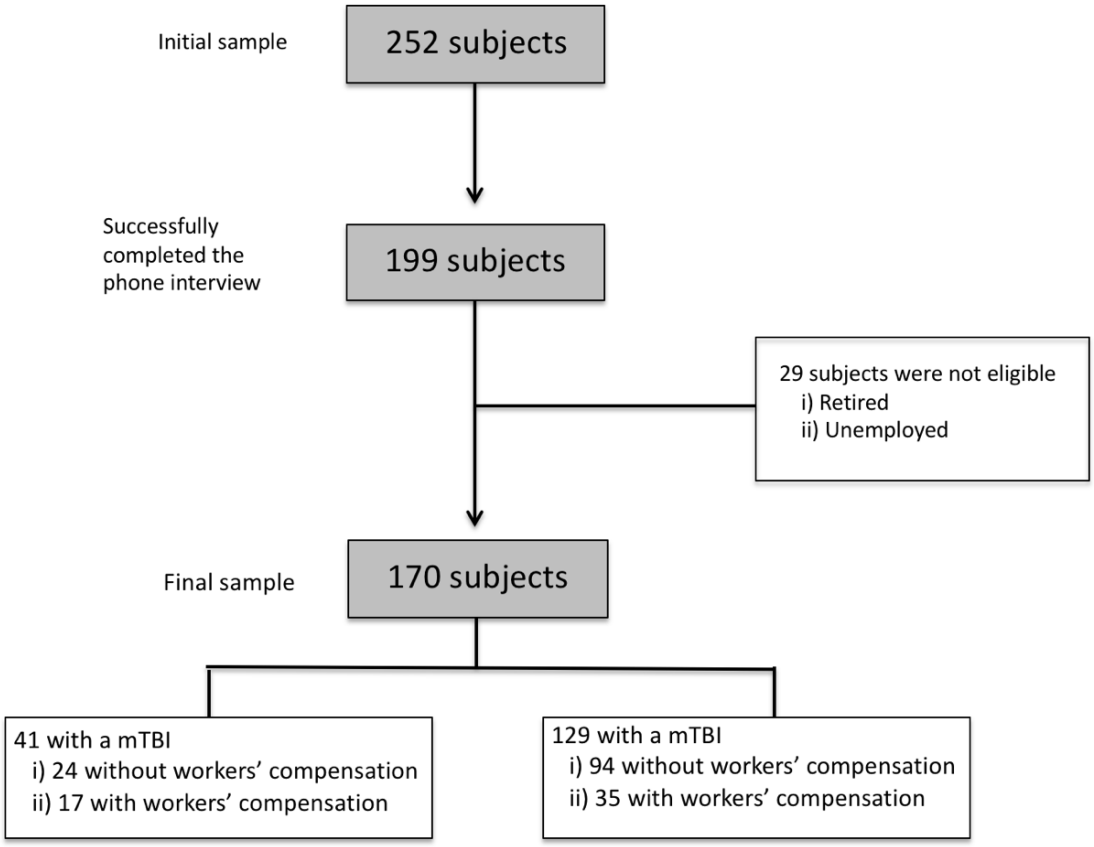
Results

Demographic characteristics of our sample are presented in Table 1. A total of 199 subjects out of 252 possible candidates were successfully contacted and agreed to complete the phone interview (see participant flowchart in Figure 1). Twenty-nine of them were retired or unemployed and therefore had to be excluded from further analyses. The remaining 170, the final sample, were all working age adults, of which 41 individuals (16 females; average age: 42.5 ± (SD = 13.9); range, 19–67) had suffered from an isolated fracture with a concomitant mTBI and 129 control patients (72 females; average age: 46.6 ± (SD = 13.4); range, 18–73) had suffered from an isolated fracture without an mTBI. The timing of the followup phone interview did not differ between groups ($p = 0.08$). Among the sample, 91 subjects (53.5%) had suffered from an upper limb fracture (i.e. clavicle, humerus, elbow, cubitus/ radius, wrist, hand), as opposed to 79 (46.5%) who had suffered from a lower limb fracture (i.e. femur, tibia/peronei, ankle, foot). More specifically, 71% (29/41) of subjects from the mTBI group suffered from an upper limb fracture compared to 48% (62/129) for the control group. The distribution was as follows: wrist (6 mTBI vs 36 non mTBI); humerus (4 mTBI vs 19 non mTBI); clavicle (16 mTBI vs 4 non-mTBI); elbow (2 mTBI vs 3 non mTBI) cubitus/radius (1 mTBI vs 2 non-mTBI); hand (0 mTBI vs 1 non mTBI); femur (1 mTBI vs 1 non mTBI); tibia/peronei (6 mTBI vs 12 non mTBI); ankle (3 mTBI vs 38 non mTBI); foot (2 mTBI vs 13 non mTBI). The remaining 53 subjects (25 females; average age: 48.8 ± (16.5)) who could not be contacted (46/53 subjects) or who refused (7/53 subjects) to complete the phone interview were demographically comparable to the two experimental groups in terms of age ($p = 0.11$) and sex ($p = 0.17$). A total of 41.4% subjects (17/41) received workers' compensation in the mTBI group as opposed to 27.1% subjects (35/129) in the control group.

Tableau 1. – Descriptive characteristics of study cohort groups

	Mild TBI	**No TBI**	**p-value comparing mTBI and no TBI**
N (*subjects*)	41	129	
Age *(years ±SD)*	42.5 ± 13.9	46.6 ± 13.4	
Sex *(Female [%])*	16 (39.0)	72 (55.8)	
Times since accident *(months±SD)*	23.0 (12.0)	20.0 (8.4)	F=3.01; (0.08)
Compensation status *(subjects [%])*	17 (41.5)	35 (27.1)	X^2= 2.61; (0.11)
Annual income (Canadian dollars)			
[24 999$ or less]	14 (34.1)	29 (22.4)	
[25 000$ - 49 999$]	10 (24.4)	47 (36.4)	
[50 000$ - 69 999$]	6 (14.6)	27 (20.9)	
[70 000$ - 99 999$]	7 (17.1)	17 (13.2)	
[100 000$ - 499 999$]	4 (9.8)	9 (6.9)	
[500 000$ or more]	0 (0)	0 (0)	

Figure 1. – Participant flowchart



Number of days taken to return to work

A total of 19.5% (8/41) of subjects with a concomitant mTBI had not returned to the work on the day of the phone interview as opposed to 6.34% (8/129) of subjects without an mTBI ($p = 0.01$). Among them, 50% (4/8) of the mTBI group were under workers' compensation compared to 88% (7/8) of the non-TBI group ($p = 0.11$). The mTBI group took on average 329.7 (SD = 298.0; range, 7–1359 days) days before returning to work after the injury, as opposed to 150.3 (SD = 171.3; range, 0–874 days) days for the control group ($p = 0.001$), after controlling for the delay between the date of the accident and the date of the phone interview (see Table 2). When subjects under workers' compensation were excluded from the analysis (N = 52; 17 with an mTBI and 35 with no mTBI), the mTBI

group still missed significantly more days of work (M = 299.4 days; SD = 333.0; range, 7–1359 days) in comparison to the control group (M = 105.2 days; SD = 121.6; range, 0– 730 days) ($p < 0.0001$) after controlling for the delay between the date of the accident and the date of the phone interview. Sex ($F = 7.5$; $p = 0.007$), but not age ($F = 0.1$; $p = 0.79$), significantly affected RTW delay based on the ANCOVA, such that women took significantly more time than men before returning to work (Table 3). Lastly, the potential impact of annual income on RTW was not subjected to statistical analyses due to large interindividual heterogeneity in the context of small sample size.

Tableau 2. – Number of days taken to return to work by group

	Mild TBI	**No TBI**	**F (p value)**
Number of days *(Days±SD)*			
a) With workers'compensation	329.7 (298.0)	150.3 (171.3)	11.29 (p=0.001)*
b) No workers' compensation	299.4 (333.0)	105.2 (121.6)	12.89 (p <0.0001)*

Level of significance was set at p<0.05*

Tableau 3. – Impact of age and sex on RTW

	F	**value**
Age		
a) With workers' compensation	0.1	.0.79
b) No Workers' compensation	1.12	.0.29
Sex		
a) With workers' compensation	7.5	0.007*
b) No Workers' compensation	2.1	0.15

Level of significance was set at p<0.05*

Discussion

The present study aimed to document the number of days taken to RTW after an isolated limb fracture among individuals who had suffered from a concomitant mTBI compared to individuals without an mTBI. The results of the study show that subjects with a concomitant mTBI take more than twice the time to RTW, a delay estimated at 329.7 days compared to 150.3 days for orthopaedic patients without an mTBI. After controlling for workers' compensation, delay to RTW was nearly three times more for patients with an mTBI (299.4 days) than for patients with no mTBI (105.2 days). Furthermore, this study shows that almost one out of five (19.5%) patients with an mTBI had not fully recovered and did not RTW at the time of the interview, as compared to 6% in the control group. These findings strongly indicate that mTBI increases work disability by preventing working age individuals from rapidly returning to work.

With the high prevalence of isolated limb fracture and mTBI, the excessively prolonged work disability found in the studied population is a sizeable social issue particularly as it afflicts a disproportionate number of workers during their peak productivity years. Delaying RTW may put these patients at an increased risk of developing additional health related issues as employment is a known protective factor against physical, psychological, and general health ailments (van der Noordt, H, Droomers, & Proper, 2014). This is particularly concerning in patients with an mTBI as they are already at high risk of psychological and general health complications and may therefore suffer more if RTW is delayed (Bryant et al., 2010).

Evidence from the present study suggests that sustaining a concomitant mTBI complicates functional recovery and therefore prevents orthopaedic patients from going back to work more rapidly. Knowing that physical and cognitive symptoms are major obstacles to functional recovery in mTBI (Carroll, Cassidy, Peloso, et al., 2004), it appears plausible that these symptoms added to those associated with the isolated limb fracture further delay RTW. Furthermore, a recent extensive review showed that mTBI can induce bodily pain in 64% of the sampled population (Mollayeva, Cassidy, Shapiro, Mollayeva, & Colantonio,

2017) in similar ways that it can also lead to motor function impairments (De Beaumont, Tremblay, Poirier, Lassonde, & Theoret, 2012; Miller et al., 2014; Parker, Osternig, van Donkelaar, & Chou, 2007). In the present study, subjects from both groups reported residual peripheral pain as well as motor function impairments as the two main reasons delaying RTW. Importantly, none of the patients from the mTBI group identified symptoms specific to post-concussion syndrome such as headaches, difficulty concentrating, sensitivity to light or sound, as determinant factors preventing RTW. Excessive fatigue, however, was noted among important factors delaying RTW, but the latter symptom was equivalently reported in both groups. In light of these findings, there is little evidence to support the involvement of post-concussion syndrome in delaying RTW in the mTBI group.

Interestingly, the 105.2 days taken to RTW in the group of isolated limb fracture patients without an mTBI parallels previous reports in milder forms of orthopaedic injury (Sluys et al., 2016). While recent estimates indicate that recovery time and RTW following an mTBI also range between 3 and 6 months, the near 10-month delay before returning to work in cases of isolated limb fracture with a concomitant mTBI is alarmingly long, especially that the vast majority of individuals in our sample were middleclass workers who did not benefit from workers' compensation. Although future studies will be needed to explain the action mechanisms of this near 6-month additional RTW delay in orthopaedic patients with concomitant mTBI, the current study findings show that mTBI and isolated limb fracture synergistically interact to cause further interference on the time taken to RTW. Although highly speculative, the known effects of mTBI and isolated limb fracture on pain are likely to be additive so as to cause individuals with combined injuries to reach the disability threshold for a longer period of time than individuals with a single injury. Additionally, it appears plausible that the debilitating cognitive symptoms after mTBI could interact with physical and pain symptoms after an orthopaedic trauma to further complicate recovery in individuals with combined injuries.

Importantly, a major issue with mTBI is that it often goes undiagnosed among both the general population and the orthopaedic community (Buck, 2011; Jodoin et al., 2016), such

that a significant proportion of orthopaedic patients may experience prolonged recovery due to mTBI symptoms that are not medically addressed. Although RTW is considered a tangible indicator of rehabilitation effectiveness (Harrison & Allen, 2003), patients suffering from an isolated limb fracture with an undetected mTBI may not be directed to the specialized resources to facilitate a prompt recovery by treating both injuries.

A limitation to this study is that RTW success was not considered. Although RTW is an important indicator of functional recovery, some patients may experience residual disabilities after injury that prevent them from returning to previous duties, thereby potentially forcing them to modify their work environment or simply change employment. Results from this study should be interpreted with caution as data was collected from a single Level I Trauma Hospital. Furthermore, although effect sizes were large enough to obtain highly significant between-groups differences, the size of the mTBI group was limited, and even more so after removing subjects under workers' compensation. Furthermore, due to the limited sample size, we were unable to stratify according to types of employment (for example, according to levels of physical or mental demand). Finally, future studies should account for additional factors, such as injury severity, education, psychological well-being, catastrophic thinking, surgical procedures and pre-injury conditions, as they are known to impact RTW (Das, Mohapatra, & Mohapatra, 2012; Drake, Gray, Yoder, Pramuka, & Llewellyn, 2000; Shi et al., 2014; Shields et al., 2016).

In conclusion, study findings highlight that having sustained a concomitant mTBI in working-age patients suffering from an isolated limb fracture significantly delays RTW. Patients with an mTBI are absent from work nearly three times longer than their peers without an mTBI, when controlled for workers' compensation. This is particularly alarming since our sample consists of individuals who are looking to go back to work but are unable to do so since their injury. The impact of mTBI on RTW warrants further attention considering both the individual and societal burden and the high productivity costs associated with work absenteeism.

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Article 4: Investigating the incidence and magnitude of heterotopic ossification with and without joints involvement in patients with a limb fracture and mild traumatic brain injury

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Abstract

Objectives: This study seeks to evaluate the incidence rate of heterotopic ossification (HO) formation in patients afflicted by an isolated limb fracture (ILF) and a concomitant mild traumatic brain injury (mTBI).

Methods: The current study is an observational study including ILF patients with or without a concomitant mTBI recruited from an orthopaedic clinic of a Level 1 Trauma Hospital. Patients were diagnosed with a mTBI according to the American Congress of Rehabilitation Medicine (ACRM) criteria. Radiographs taken on average 3 months post-trauma were analysed separately by two distinct specialists for the presence of HO proximally to the fracture site (joints or extra joints). Both raters referred to Brooker's and Della's Valle's classification to establish signs of HO. First, analyses were conducted for the full sample. Secondly, a matched cohort was used in order to control for specific factors, namely age, sex, type of injury, and time elapsed between the accident and the analyzed radiograph.

Result: The full sample included a total of 183 patients with an ILF (94 females; 47.5 years old), of which 50 had a concomitant mTBI and 133 without. Radiographic evidence of HO was significantly higher in patients with an ILF and a mTBI compared to ILF patients (X^2=6.50; p=0.01). The matched cohort consisted of 94 participants (i.e.; 47 patients from the ILF+mTBI group and 47 patients from the ILF group). Again, ILF+mTBI patients presented significantly higher rates of HO signs in comparison to ILF patients (X^2=3.69; p=0.04). Presence of HO was associated with prolonged delays to return to work (RTW) only in ILF+mTBI patients (F=4.055; p=0.05) but not in ILF patients (F=0.823; p=0.37).

Conclusions: Study findings suggest that rates of HO are significantly higher proximally to fracture sites when ILF patients sustain a concomitant mTBI, even after controlling for factors known to influence HO. Moreover, results show that HO is associated with a prolonged RTW only in ILF patients with a concomitant mTBI but not in ILF-only patients. The impact of mTBI on HO formation warrants further attention to

detect early signs of HO, to identify shared physiopathological mechanisms and, ultimately, to design targeted therapies.

Introduction

Heterotopic ossification (HO), defined as an abnormal bone formation occurring in extra-skeletal tissues, is a possible complication following fractures (Kaplan, Glaser, Hebela, & Shore, 2004). The risk of developing HO varies depending on the type of fracture, with incidence of HO reaching nearly 40% in patients with elbow fractures (Eisenstein, Stapley, & Grover, 2018; Foruria, Augustin, Morrey, & Sanchez-Sotelo, 2013; Foruria, Lawrence, Augustin, Morrey, & Sanchez-Sotelo, 2014). HO develops around the fracture site, more typically near a joint, making certain fractures, such as elbow and hip fractures, more prone to HO formation (Pape, Marsh, Morley, Krettek, & Giannoudis, 2004). As a result, most studies have investigated HO in this context and the impact of fractures occurring away from joints on HO remains less known.

Clinical manifestations of HO, including soft-tissue loss, joint contractures, motion deficits, stiffness, and chronic pain, can become a debilitating condition for the affected patients (Vanden Bossche & Vanderstraeten, 2005). HO has been associated with reduced quality of life mainly due to extended medical treatment and higher probability of undergoing additional surgical procedures to remove heterotopic bone (Winkler et al., 2015). It is therefore not surprising that HO has been identified as a major obstacle to rehabilitation (Nauth et al., 2012).

HO initially follows similar physiological patterns as the natural fracture healing process (Nauth et al., 2012). However, HO's pathological mechanisms are thought to originate from the convergence of multiple factors including prolonged nervous system and immune system responses to injury (Convente, Wang, Pignolo, Kaplan, & Shore, 2015; Forsberg, Potter, Polfer, Safford, & Elster, 2014; Kraft et al., 2016; Sullivan, Torres, Mehta, & Ahn, 2013). More precisely, recent studies suggest that HO results from exaggerated inflammatory cytokine release, osteoprogenitor cell proliferation due to inflammation, increased leptin levels, vascularization of injured tissues, and the activation of bone morphogenic protein (BMP) signaling, all known to promote bone formation in extra-

skeletal locations (Eisenstein et al., 2018; Firoozabadi, Alton, & Sagi, 2017; Nauth et al., 2012).

Traumatic brain injury (TBI) is a known risk factor for the development of HO in polytrauma patients (Bajwa, Kesavan, & Mohan, 2018; Coelho & Beraldo, 2009; Dizdar et al., 2013; Ranganathan et al., 2015). Recent estimates suggest that nearly 20% of patients who suffer from TBI or spinal cord injuries will develop HO (Cipriano et al., 2009). Moreover, concomitant limb fracture and TBI is associated with a twofold increase risk of HO occurrence (Dizdar et al., 2013; Foruria et al., 2014). A possible explanation for the high occurrence of HO in orthopedic patients with a TBI is the overlapping physiopathological mechanisms involved in both injuries, namely dysfunctions in the blood-brain barrier permeability, substance P increase, and prolonged pro-inflammatory cytokine release, making the physiological environment more prone to HO formation. (Evans et al., 2012; Huang et al., 2018). These pathological mechanisms are also observed after the mildest form of TBI, the mild TBI (mTBI).

MTBIs account for approximately 70-90% of all TBIs sustained and are frequent among patients who suffered from fractures, with an incidence rate estimated at 23% (Cassidy et al., 2004; Jodoin et al., 2016). Although considered the mildest form of TBIs, a growing body of evidence shows that concomitant mTBI can have a significant impact on recovery in patients with fractures, highlighting the importance of considering the interaction between these two injuries (Jodoin, Rouleau, Gosselin, et al., 2017; Jodoin, Rouleau, Larson-Dupuis, et al., 2017). To our knowledge, the association between mTBI and HO has not been investigated. Lack of medical follow-ups after mTBIs, subclinical HO signs associated with less severe accidents as well as underdiagnosed mTBI in trauma patients presenting with fractures could partly underlie this lack of scientific interest (Jodoin et al., 2016). Here, we tested whether isolated limb fracture (ILF) patients presenting with a concomitant mTBI have a higher incidence rate of HO when compared to ILF patients without a mTBI.

Methods

Participants selection

All participants included in this study were selected from a previous sample recruited consecutively from a single orthopedic clinic of a Level 1 Trauma Hospital to evaluate the incidence rate of mTBI among ILF patients (For more details; (Jodoin et al., 2016). Each participant has consented to grant access to their research data for future studies. This sample consisted of 251 participants with an ILF of which 58 participants had suffered from a mTBI based on the American Congress of Rehabilitation Medicine (ACRM) clinical criteria (loss of consciousness, loss of memory for the events immediately before or after the accident, and alteration of mental state at the time of the accident) (Carroll et al., 2004). A mTBI diagnosis was given when a patient reported at least three of the four abovementioned criteria. Moreover, patients' medical files were also screened to gather more information related to the accident and to the injuries. Patients were eligible to take part in this study if they had suffered from an ILF and did not meet any of the exclusion criteria, namely being under 18 years old, substance-related intoxication at the emergency room, Glasgow Coma Scale under 13 at emergency admission, health-related complications other than mTBI in the acute and post-acute injury phases, and non-extremity fractures (hip, pelvis, ribs, neck, spinal cord, and skull). Moreover, patients were excluded from the analyses if they presented with signs of HO prior to the accident and if raters were unable to distinguish between bone fragment and HO. The study was approved by a local ethics committee.

Characterization of HO

Participants were included from the initial sample only if radiographs were taken at least 45 days post-trauma. This cut-off was set as signs of HO can be adequately detected at that time (Cipriano et al., 2009). Moreover, in cases of multiple radiograph availabilities for a single patient, the radiograph conducted the closest to three months post-trauma was selected considering that medical check-ups are frequent at this time and that it falls within the range when HO formation is typically best detected (Cipriano et al., 2009). Radiographs of all patients were analysed separately by a trained senior orthopaedist

resident and a senior orthopedic surgeon both blind to the subjects' group classification. To evaluate signs of HO, both raters used a specialised radiology display system (NEC Display Solutions; MultiSync Monitor LCD 2090UXi-20.1; Made in China) to detect the presence of abnormal bone formation located in extra-skeletal soft tissues. More specifically, signs of HO were sought for near the fracture location, independently of joints involvement (See Figure 1 for a representative case of HO among the current sample). Hypertrophic callus was excluded from HO cases as the ossification identified needed to be at the heterotopic site and not at the fracture callus itself. In addition, Brooker's and Della Valle's classifications were used conjointly as suggested by Toom and colleagues (2005) aiming to improve inter-observer reliability in the assessment of HO. Inter-rater reliability was verified and reached an almost perfect agreement according to Cohen's kappa coefficient (k=0.93). In case of disagreements among raters, both raters reviewed together the radiograph to reach an agreement concerning the presence of HO formation.

Figure 1. – Representative case of HO among sample

Matched sample procedure

Further steps were taken to control for potential factors known to affect the risk of HO formation. Patients from the ILF+mTBI group were matched with ILF patients according to age, sex, type of injury (area of fracture), and time elapsed between the accident and the radiograph. The importance of matching for the delay between the accident and the analyzed radiograph is to control for the risk of HO signs developing after the analysed radiograph (Cipriano et al., 2009). To do so, we proceeded by using a one-on-one matching approach based on the following criteria: 1) age ($\pm$5 years); 2) sex; 3) type of injury (area of fracture); 4) time elapsed between the accident and the radiograph ($\pm$14 days). A match was made when all four criteria corresponded for two participants from each experimental group (ILF+mTBI group and ILF group). When more than one participant from the control group matched with a ILF+mTBI patient based on the aforementioned criteria, we selected the control participant who corresponded most closely to the ILF+mTBI patient. This matching process allowed to form 47 near-identical pairs. The remaining participants who were not matched according to the criteria were excluded from these analyses.

Analyses

Descriptive analyses were used to characterize and compare the two groups from our study (ILF+mTBI group and ILF group). Results from descriptive analyses are expressed as means, SD (standard deviation), and percentages (refer to tables 1-2). We used Pearson chi-square tests to compare the incidence rate of HO between the two experimental groups (ILF+mTBI group and ILF group). Additional chi-square analyses were conducted to evaluate the possible impact of sex, age group (18-24; 25-44; 45-64; 65+ years old), joint involvement (periarticular fracture versus diaphyseal fracture) and surgical procedures on HO formation. A linear regression analysis was computed to give an estimate on which independent variable, mTBI or joint involvement, best predicted HO development. Statistical tests were carried out with a α-level fixed at 0.05. The same pattern of analyses was used to test the study hypothesis among the matched sample.

Moreover, a 2X2 ANOVA was used to assess the impact of HO and mTBI on return to work (RTW) among the matched sample. RTW was used in this study to reflect potential impact of HO development on functional outcome as it is known to be a good marker of recovery (Clay, Newstead, Watson, & McClure, 2010). Information on RTW was collected in the context of a previous study conducted by our group using the same sample (See Jodoin, Rouleau, Larson-Dupuis, et al., 2017 for more details). Statistical analyses were performed using IBM SPSS software version 24 (Armonk, NY, United States).

Results

Results of full sample analysis

A total of 183 participants were selected, from a study cohort of 251 individuals recruited by our group (See participant flowchart in Figure 2). The remaining participants were excluded from the current study due to the inability to access their radiograph. Among the final sample, 50 patients were in the ILF+mTBI group (females=19; mean age=43.8) and 133 patients were in the ILF group (females=75; mean age=48.9). On average, radiographs were analysed 86.8 days post-trauma (range: 45 days – 201 days), a delay that was similar between groups (F=0.01; p=0.92) (See table 1). There was a significantly higher rate of periarticular fractures, as opposed to diaphyseal fractures, in the ILF group compared to the ILF+mTBI group (X^2=16.69; p=0.01) (See table 2). This difference can be mainly attributed to the low rate of ILF+mTBI patients with ankle and distal radius fractures, compared to the ILF patients. Given the higher incidence of mTBI in fractures occurring proximally to the head (Jodoin et al., 2016), risks of suffering from a mTBI are rare in individuals treated for ankle and distal radius fractures.

Figure 2. – Participant selection flowchart

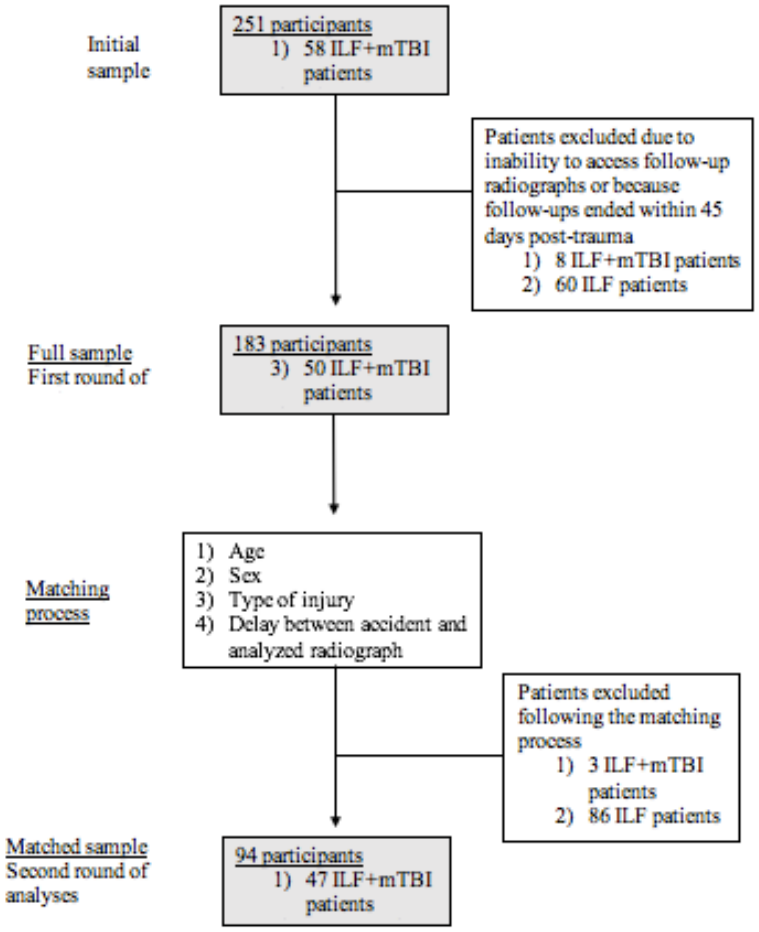

Tableau 1. – Descriptive characteristics of full study cohort by group

	Total	**mTBI**	**No TBI**	**P-value**
N *(subjects)*	183	50	133	-
Age (*years [SD]*)	47.5 (15.5)	43.8 (15.3)	48.9 (15.3)	0.75
Sex (*Female [%]*)	94 (51.4)	19 (38.0)	75 (56.4)	0.02*
Surgical procedures (*% of sample*)	32.7	26.8	34.6	0.23
Delay between trauma and analyzed radiograph (*days*)	86.8	87.2	86.7	0.92

Level of significance was set at p<0.05*

Tableau 2. – Distribution of fracture characteristics

	Total	**mTBI**	**No TBI**	
Body distribution of fractures *[Number of patients]*				
- Metacarpal	2	1	1	
- Metatarsal	11	3	8	
- Proximal humerus	21	7	14	
- Humerus diaphysis	5	1	4	
- Distal humerus	6	0	6	
- Scapula	3	2	1	
- Clavicle	18	11	7	
- Proximal ulna	5	2	3	
- Ulna diaphyseal	3	2	1	
- Distal radius	45	8	37	
- Femur	2	1	1	
- Patella	2	1	1	
- Proximal tibia	4	2	2	
- Diaphyseal tibia	7	3	4	
- Distal tibia	9	2	7	
- Ankle	40	4	36	
Joint involvement				**P-value**
- **Yes** (periarticular fracture)	146	30	116	0.01*
- **No** (diaphyseal fracture)	37	20	17	

Level of significance was set at p<0.05*

Patients in the ILF+mTBI group showed significantly more signs of HO compared to patients with an ILF alone (X=6.50; p=0.01), with the majority of patients presenting with low grade HO according to Brooker's and Della's Valle's classification (See tables 3-4). The incidence rates of HO signs were 46.0% in ILF+mTBI patients (23/50) as opposed to 26.3% in patients with an ILF alone (35/133). Of note, sex (X^2=2.32; p=0.10), age group (X^2=2.08;

p=0.56), and surgical procedures (X^2=1.71; p=0.13) were unrelated to the detection of signs of HO. Furthermore, rates of HO signs were found to be similar whether the fracture occurred proximally (periarticular fracture) or distally (diaphyseal fracture) to a joint (X^2=1.68; p=0.24). See table 5 for more details. Lastly, results from the computed linear regression analysis show that sustaining a concomitant mTBI significantly predicted risks of HO development (β-coefficient=0.18; t=2.29; p=0.02), whereas joint involvement was unrelated to HO development (β-coefficient=-0.05; t=-0.56; p=0.58).

Tableau 3. – HO signs among full sample

	mTBI	**No TBI**	**X^2**	**P-Value**
HO signs (*Number of patients [%]*)	23/50 (46.0)	35/133 (26.3)	6.50	0.01*

Level of significance was set at p<0.05*

Tableau 4. – Identification of HO according to Brooker's and Della Valle's classifications

	Total	**mTBI**	**No TBI**
Number of subjects per classification			
- ***A0*** ***Absence of ossification***	124	24	100
- ***A1*** ***Isolated ossifications less than 1cm in length***	46	20	26
- ***B1*** ***Isolated ossifications at least 1cm in length – leaving MORE than 1cm distance between pelvis and femur***	2	2	0
- ***B2*** ***Marginal ossifications – leaving MORE than 1cm distance between pelvis and femur***	3	0	3
- ***C1*** ***Isolated ossifications at least 1cm in length – leaving LESS than 1cm distance between pelvis and femur or ankylosis***	3	2	1
- ***C2*** ***Marginal ossifications – leaving LESS than 1cm distance between pelvis and femur or ankylosis***	4	2	2
- ***C3*** **Ankylosis –** ***leaving LESS than 1cm distance between pelvis and femur or ankylosis***	1	0	1

Tableau 5. – Risks of HO in relation to joint involvement

	Periarticular fracture	**Diaphyseal fracture**	**P-value**
mTBI - *Number of subjects with HO [%]*	14/30 (46.7)	9/20 (45.0)	0.57
No mTBI - *Number of subjects with HO [%]*	29/116 (25.0)	6/17 (35.3)	0.38
P-value	0.02*	0.40	

Level of significance was set at p<0.05*

Results of analyses from the matched sample

A total of 94 participants were matched (i.e.; 47 patients from the ILF+mTBI group and 47 patients from the ILF group). Participants from both groups were equivalent according to the following criteria: age (t=0.00; p=1.00), sex (X^2=0.00; p=1.00), area of injury (X^2=0.00; p=1.00), and delay between the accident and the analyzed radiograph (t=1.08; p=0.30). Groups did not differ based on rates of surgical procedures (X^2=1.73; p=0.25). Refer to Table 6 to obtain detailed descriptive characteristics regarding the matched sample.

Similar to results obtained with the full sample, HO incidence was significantly higher in ILF+mTBI patients in comparison to ILF patients (X^2=3.69; p=0.04) (See table 7). This result further supports the notion that concomitant mTBI puts ILF patients at greater risk of developing HO. More specifically, 46.8% of ILF+mTBI patients (22/47) from the matched sample presented signs of HO compared to only 27.7% in ILF patients without a mTBI (13/47). Presence of HO negatively impacted RTW delays in patients with ILF+mTBI (F=4.055; p=0.05). Return to work delays did not statistically differ according to the presence of HO in ILF patients without a comorbid mTBI (F=0.823; p=0.37). More specifically, ILF+mTBI patients with HO took, on average, 379 days to RTW compared to 106 days for ILF patients with HO but without a mTBI. As for ILF+mTBI patients without

HO, it took, on average, 214 days to RTW as opposed to 168 days for ILF patients without HO and mTBI.

Tableau 6. – Descriptive characteristics of matched sample by group

	Total	**mTBI**	**No TBI**	**P-value**
N *(subjects)*	94	47	47	-
Age (*years [SD]*)	43.5 (15.1)	43.5 (15.5)	43.5 (14.7)	1.00
Sex (*Female [%]*)	34 (36.2)	17 (36.2)	17 (36.2)	1.00
Surgical procedures (*% of sample*)	33.7	26.3	40.0	0.25
Delay between trauma and analyzed radiograph (*days*)	92.4	98.8	86.1	0.30

Level of significance was set at p<0.05*

Tableau 7. – HO signs among matched sample

	mTBI	**No TBI**	**X^2**	**P-Value**
HO signs (*Number of patients [%]*)	22/47 (46.8)	13/47 (27.7)	3.69	0.04*

Level of significance was set at p<0.05*

Discussion

This study investigated the incidence rate of HO among ILF patients with or without a concomitant mTBI. Results from the present study suggest that presence of HO is significantly higher in patients with both trauma injuries (mTBI and ILF) compared to ILF patients, even after controlling for factors known to influence HO, such as age, sex, area of injury, and time elapsed between the accident and the analysed radiograph. Moreover, results from linear regressions show that sustaining a concomitant mTBI significantly predicts risks for HO development whereas suffering from a fracture near a joint was unrelated. These findings are of particular interest, considering the high prevalence of

both injuries, namely ILF and mTBI, and the possible deleterious consequences of HO on recovery and quality of life. In addition, the clinical symptoms linked to HO combined with possible additional surgical procedures to remove the heterotopic bone represent staggering financial burdens (health care expenditures and loss of productivity) (Eisenstein et al., 2018).

Another striking finding from this study is that the combination of HO formation and mTBI was associated with significantly longer RTW delays after an isolated limb fracture. Of note, mTBI without HO also negatively impacted RTW in ILF patients, but to a lesser extent than in the presence of HO. Indeed, results show a near 45% increase in delays to RTW when HO signs were detected in ILF+mTBI patients compared to ILF+mTBI patients without HO. This is particularly alarming considering that almost half of the assessed patients with an ILF and a comorbid mTBI presented signs of HO. This finding points to the clinical relevance of systematically implementing a follow-up visit at least with ILF+mTBI patients if we are to investigate the impact of mTBI on clinical outcomes associated with HO such as pain, stiffness, and articular amplitude.

Most studies interested in the impact of concomitant TBI on the risk for HO formation focused on polytrauma patients or severely injured patients who suffered from a moderate to severe TBI and mostly focused on HO occurring near a joint (Bajwa et al., 2018; Boes et al., 2006; Garland, 1991a, 1991b). The present study, however, shows that patients with an injury considered less severe, such as an ILF, are significantly more vulnerable to HO formation, regardless of joint involvement, when also afflicted by a comorbid mTBI. To the best of our knowledge, this is the first study specifically investigating the impact of mTBI on HO formation among an orthopaedic population. The fact that mTBI typically receives limited medical attention beyond the acute post-accident phase can serve as a possible explanation. Another possibility could be that mTBI patients is not a clinical condition that justifies exposing uninjured bones to X-ray radiation, thus preventing the detection of HO formation in mTBI-alone patients.

From a clinical standpoint, these results shed light on the importance of accounting for the presence of mTBI when treating ILF patients considering that over 44% of patients presenting with both injuries will develop HO. HO presence is classically studied in a context of hip and elbow secondary ankylosis and severe neurological concomitant injury. Although conjectural, this study provides preliminary evidence of the significant impact of mild HO on patient outcome and extends HO screening beyond joints. Importantly, the addition of diaphyseal HO screening provides new information on whole-bone incidence rates of HO following a single fracture. Multiple factors may be at stake with regard to the higher incidence of HO among ILF+mTBI patients. For example, HO is believed to originate from the convergence of multiple mechanisms that closely involve the interaction of the immune system and the central nervous system (Convente et al., 2015; Forsberg et al., 2014; Kraft et al., 2016; Sullivan et al., 2013). More specifically, a growing body of evidence highlights the involvement of the blood-brain-barrier (BBB) in HO formation (Huang et al., 2018). Interestingly, BBB permeability dysfunction is a well-known consequence of TBI and has been identified as a cause for high incidence rates of HO in patients with moderate to severe TBIs (Toffoli, Gautschi, Frey, Filgueira, & Zellweger, 2008). Recent studies have shown that mTBI also leads to BBB dysfunction which can act as a facilitator in the central nervous system invasion of peripheral immune response substances, such as inflammatory cytokines, following a peripheral insult (Rowe et al., 2016). Additionally, neuroendocrine regulation, a system that is often deficient following mTBI, is closely involved in bone remodeling and HO formation (Undurti et al., 2018). Although speculative, it may be possible that the physiopathology of bone fracture and that of mTBI synergistically interact to promote HO formation. Shedding light on the possible involvement of physiopathological underpinnings of mTBI in HO could help identify new treatment targets and clinical management strategies aiming to minimize HO formation. In this study, HO was most frequently classified as low grade with small bone formation. This level of HO most likely does not cause decreased function by itself. We hypothesize that this low-grade HO is a sign of increased local soft tissue injury and increased neurological inflammation that is secondarily affecting outcome.

One limitation to the current study is that it uses data from participants recruited in the context of a previous study, which potentially restricts study findings generalization. Secondly, collection of prospective data should systematically control for the time elapsed since the injury at the time of radiographs (for example, all taken at three months post-accident) so as to reduce risks for missed HO diagnoses. One interesting avenue in further investigating the relation between RTW delays and HO formation would be to specify the type of work conducted (light versus heavy work) as well as the quality of the RTW (successful RTW versus work accommodations needed). Moreover, investigating RTW delays in relation with both prospective functional recovery measures and low-grade HO could help us identify therapeutic targets for optimal orthopedic trauma recovery. Given that some fractures are more prone to HO formation, larger-scale replication studies should consider data stratification analyses according to injury types. Gained knowledge would allow us to further refine classification of at-risk patients. Finally, future studies should account for additional factors, such as injury severity, duration of immobilization, and pre-injury conditions, such as, but not limited to, history of HO and genetic predisposition, as they are known to impact HO formation (Dizdar et al., 2013; Pape et al., 2004).

Conclusion

In conclusion, study findings highlight that sustaining a comorbid mTBI puts ILF patients at significantly higher risk of developing HO. Moreover, ILF patients with a mTBI are greatly impacted by HO in relation with RTW, a factor associated with high productivity costs and risks for chronic fracture injury symptoms. This is of significant clinical interest considering the high incidence of both injuries, the frequency at which mTBI goes undiagnosed, and the clinical impact of HO on recovery. The impact of mTBI on HO formation warrants further attention to detect early signs of HO, to identify shared physiopathological mechanisms and, ultimately, to design targeted therapies.

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Article 5: The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients

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Abstract

Pain is a multifaceted condition and a major ongoing challenge for healthcare professionals having to treat patients in whom pain put them at risk of developing other conditions. Significant efforts have been invested in both clinical and research settings in an attempt to demystify the mechanisms at stake and develop optimal treatments as well as to reduce individual and societal costs. It is now universally accepted that neuroinflammation and central sensitization are two key underlying factors causing pain chronification as they result from maladaptive central nervous system plasticity. Recent research has shown that the mechanisms of action of repetitive transcranial magnetic stimulation (rTMS) make it a particularly promising avenue in treating various pain conditions. This review will first discuss the contribution of neuroinflammation and central sensitization in the transition from acute to chronic pain in traumatically injured patients. A detailed discussion on how rTMS may allow the restoration from maladaptive plasticity in addition to breaking down the chain of events leading to pain chronification will follow. Lastly, this review will provide a theoretical framework of what might constitute optimal rTMS modalities in dealing with pain symptoms in traumatically injured patients based on an integrated perspective of the physiopathological mechanisms underlying pain.

Introduction

Pain is a multidimensional phenomenon consisting of complex mechanisms featuring sensory and motor components (sensory-discriminative features of pain) as well as emotional and cognitive aspects (affective-motivational processing of pain) (Davis & Moayedi, 2013; Seifert & Maihofner, 2011). According to the International Association for the Study of Pain (IASP), chronic pain is characterized as persistent pain that is experienced every day for three months over a period of six months (Merskey & Bogduk, 1994). Chronic pain constitutes a major public health concern that has deleterious effects on quality of life (Patel et al., 2012). Chronic pain afflicts, in the United States alone, > 100 million individuals suffering from a wide variety of diseases and results in more than $560 to $654 billion in total annual cost (Gaskin & Richard, 2012).

Acquired traumatic injuries represent a significant proportion of patients seeking care in the healthcare system and regroup a wide variety of injuries such as, but not limited to, musculoskeletal injuries (fractures), cranio-maxillofacial trauma (facial trauma), and traumatic brain injuries (Centers for Disease, 2011). Pain constitutes one of the most common symptoms shared among this population and is known to delay return to work even in patients suffering from minor traumas (Albrecht et al., 2013; Archer, Castillo, Wegener, Abraham, & Obremskey, 2012; MacDermid, Roth, & Richards, 2003; Platts-Mills et al., 2016). Despite intensive research, treating pain represents a particularly challenging task considering the high heterogeneity in clinical manifestations across individuals and pathologies. Furthermore, the difficulty in predicting which patients will transition from acute to chronic pain as well as the lack of consensus as to which treatment to prioritize make it an even bigger challenge for healthcare professionals. Indeed, predictors of pain chronification following an acquired traumatic injury are not well understood, which makes it even more challenging to develop effective treatments that will maximize recovery, but recent evidence suggests the involvement of maladaptive neuroplasticity mechanisms (McGreevy, Bottros, & Raja, 2011; Miranda et al., 2015). Development of interventions aiming to prevent the installation of chronic pain is critical as persistent pain is associated with an increased risk of medical complications, staggering financial burdens (on personal and societal levels) and diminished quality of life (Patel et al., 2012).

Although treating pain is considered a human right for which all healthcare professionals are responsible (Lohman, Schleifer, & Amon, 2010), this field of research is currently undergoing important transformations to address the multiple shortcomings associated with pharmacological treatments. Indeed, it is estimated that 30% of chronic pain patients remain symptomatic despite optimal treatment (Galhardoni et al., 2015). An increasing amount of alternative treatments are currently gaining in popularity in an attempt to reduce, and eventually replace, the use of the highly controversial prescription of opioids for its potentially serious side effects (Benyamin et al., 2008; Chou et al., 2015; Chou, Hickey, Sundman, Song, & Chen, 2015; Ray, Chung, Murray, Hall, & Stein, 2016). Among them, repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, appears particularly promising in alleviating pain symptoms among acquired injury patients by tackling key elements of the neurophysiopathological underpinnings of acute pain symptoms. Indeed, the modulating effects of rTMS on synaptic plasticity together with its ability to precisely target brain regions involved in pain processing has provided pain relief in several experimental pain studies (Hallett, 2000, 2007). Moreover, although very limited data exist on the clinical utility of rTMS during the acute phase, we believe that this technique would be most beneficial when applied during the early stage of the trauma given that rTMS allows to modulate the excitability of the stimulated brain region through the activation/inhibition of NMDA receptors, a central element to the excitotoxic chain reactions associated with pain chronification. To support this opinion, we will first provide a detailed description of two of the main mechanisms involved in pain chronification, namely central sensitization and neuroinflammation, in a context of acquired injuries. Secondly, this review will discuss the available literature on the mechanisms involved in rTMS as a potential treatment for reducing the risk of transition from acute to chronic pain. Furthermore, this review will provide a theoretical framework of what could reveal to be optimal rTMS modalities in order to reduce pain based on an integrated perspective of the physiopathological mechanisms underlying pain in acquired injury patients.

Mechanisms of central sensitization

Central sensitization is a pain-facilitatory state resulting from the amplification of membrane excitability and synaptic efficacy within the central nervous system (CNS) (Koltzenburg, Torebjork, & Wahren, 1994; Latremoliere & Woolf, 2009). The resulting chain reaction makes the brain overly reactive (sensory amplification) to noxious stimuli (pain hypersensitivity and hyperalgesia) and non-noxious stimuli (allodynia) (Baron, Binder, & Wasner, 2010; Latremoliere & Woolf, 2009; Sandkuhler, 2009; Woolf, 2011). When the tissue or nerve insults result from peripheral damage, such as following a fracture, this central mechanism of pain chronification mainly occurs as a consequence of both peripheral and central nervous system markers (Clauw, 2015; McGreevy et al., 2011). Indeed, nociceptors at the site of injury become overly activated due to inflammation, which creates short-lasting synaptic plasticity called "wind-up" within the spinal cord (D'Mello & Dickenson, 2008; Herrero, Laird, & Lopez-Garcia, 2000). This phenomenon mainly results from excitatory amino acids and neuropeptides release taking place via the spinothalamic tract of the dorsal horn in the spinal cord ultimately leading to excitotoxicity (D'Mello & Dickenson, 2008; Xu, Liu, Hughes, & McAdoo, 2008). Excitotoxicity is defined as prolonged overactivation of excitatory neurotransmitters such as glutamate and can lead to neuronal damage or death (Yi & Hazell, 2006). The excitotoxicity state occurring within the spinal cord also facilitates the transitioning of nociceptive afferent signals to the brain (Hanakawa, 2012) resulting in central sensitization.

Multiple other pain-facilitating mechanisms are at stake in central sensitization, such as overactivation of *N*-methyl-d-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Hains, Saab, Klein, Craner, & Waxman, 2004; Ultenius, Linderoth, Meyerson, & Wallin, 2006). The up regulation of NMDA receptors, a type of glutamate receptor, triggers and facilitates peripheral and central sensitization by lowering the firing threshold, therefore making the spinal cord overly reactive to pain stimuli (Latremoliere & Woolf, 2009; Petrenko, Yamakura, Baba, & Shimoji, 2003). Similarly, up-regulated AMPA receptors also contribute to increasing nociceptive synaptic plasticity within the spinal cord (Garry et al., 2003), but more so during the initial acute phase (D'Mello & Dickenson, 2008; Voscopoulos & Lema, 2010). There is also an increased activation of voltage-gated sodium channels in the second-order

nociceptive neurons, which act as facilitators for glutamate and substance P release (Luo et al., 2001), further promoting an excitatory state (Naro et al., 2016). Furthermore, this excitatory state also negatively affects GABAergic activity within the CNS (the spinal cord and the cortex), the main inhibitory neurotransmitter of the human body, which can no longer produce sufficient inhibitory influence to compensate for the excessive excitability and play its usual neuroprotective role (Baba et al., 2003; Lin, Peng, & Willis, 1996). For this reason, inefficient GABA inhibition further contributes to central sensitization (Baron et al., 2010; Castro-Lopes, Tavares, & Coimbra, 1993). Indeed, GABAergic transmission and efficacy are suppressed by overly represented NMDA receptors and their excitatory neurotoxic effects, which eventually lead to disinhibition (Latremoliere & Woolf, 2009). This is supported by studies showing that NMDA receptor antagonists can successfully reduce various central sensitization symptoms such as allodynia (painful reaction to non-noxious stimuli) and hyperalgesia (exaggerated reaction to pain in response to noxious stimuli) (Bennett, 2000). Unfortunately, long-term use of NMDA receptors-based substances is contraindicated due to adverse non-specific side effects (Niesters, Martini, & Dahan, 2014) but they remain an important therapeutic target (Corasaniti, Amantea, Russo, & Bagetta, 2006). Taken together, secretion of excitatory neuropeptides and amino acids within the dorsal horn and reduction of inhibitory mechanisms generate an unbalanced state within the CNS, which represents a putative risk for developing central sensitization and maladaptive neuroplasticity (Naro et al., 2016; Petrenko et al., 2003).

Other studies have shown that ongoing excitatory discharge in chronic pain induces LTP-like synaptic plasticity changes (Nijs et al., 2015), which ultimately give rise to maladaptive plasticity. The latter was recently associated with significant facilitation of neuronal pain transmission and, again, possibly excitotoxicity (Costigan, Scholz, & Woolf, 2009). Interestingly, transcranial magnetic stimulation (TMS) applied over the primary motor cortex (M1) allows the modulation of long-term potentiation (LTP) and long-term depression (LTD) mechanisms, therefore appearing as a highly pertinent and reliable measure for studying the mechanisms involved in central sensitization (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Of note, glutamatergic and GABAergic neurotransmission play a key regulating role on LTP and LTD bidirectional plasticity

mechanisms (Caillard, Ben-Ari, & Gaiarsa, 1999; Hasan et al., 2012; Pavlov, Lauri, Taira, & Rauvala, 2004). Most chronic pain studies describe a disinhibition state partly due to deficiency in GABA-dependent intracortical inhibition (ICI) and the latter is associated with the intensity of pain levels (Caumo et al., 2016; Lefaucheur, Drouot, Menard-Lefaucheur, Keravel, & Nguyen, 2006; Lenz et al., 2011; Mhalla et al., 2011; Parker, Lewis, Rice, & McNair, 2016; Schwenkreis et al., 2010). Accordingly, TMS markers of cortical excitability strongly correlate with the magnitude of pain, depression, catastrophizing, motor deficits and fatigue (Mhalla et al., 2011). In the latter study, cortical excitability restoration following a 14-day rTMS protocol was associated with significant symptoms relief including pain symptoms. Furthermore, brain-derived neurotrophic factor (BDNF), a protein capable of modulating neuronal excitability (Desai, Rutherford, & Turrigiano, 1999), can further promote the process of pain chronification from a very early stage following the injury (Caumo et al., 2016). Indeed, BDNF has the potential to increase levels of available excitatory neurotransmitters (glutamate), or LTP, as well as to inversely reduce levels of inhibitory neurotransmitters (GABA) within the spinal cord and the brain (Caumo et al., 2016; Nijs et al., 2015; Smith, 2014). Given that BDNF is indiscriminately release immediately after an acquired brain injury, BDNF is believed to play a central role in the formation of maladaptive synaptic connections and thus contribute to the diffuse brain response seen during chronic pain installation.

At the brain level, the “pain matrix”, a cortical network specifically involved in the perception of pain (primary (S1) and secondary (S2) somatosensory cortex, insula, anterior cingulate cortex, thalamus, dorsolateral prefrontal cortex (DLPFC) and basal ganglia), becomes overly activated due to persistent maladaptive neuroplasticity and associated cortical reorganization (Gracely, Petzke, Wolf, & Clauw, 2002; Henry, Chiodo, & Yang, 2011; Legrain, Iannetti, Plaghki, & Mouraux, 2011; McGreevy et al., 2011; Napadow, Kim, Clauw, & Harris, 2012; Nijs et al., 2015; Olivan-Blazquez et al., 2014; Seifert & Maihofner, 2009). Persistent pain also exerts functional reorganization within the sensorimotor cortex by reducing gray matter density but also by modifying functional connectivity between the insula, a key structure responsible for the emotional-cognitive component of pain, and other brain regions (Baliki et al., 2012). Accordingly, it has been shown that the level of pain experienced by patients is closely related to the level of

cortical reorganization. Indeed, restoring brain function to normal levels was found to reduce pain perception and to improve quality of life (Chapman & Vierck, 2016; Passard et al., 2007). Furthermore, there is also a shift from inhibitory to excitatory-dominant activity within the endogenous pain modulatory descending pathway of the spinal cord during pain chronification, which again increases nociceptive transmission (Vanegas & Schaible, 2004). Indeed, the spinal cord appears to play a major role in maintaining pain states, such that it contributes to the spreading of excitatory activity both via the ascending and the descending pathways. Interestingly, studies have shown that descending facilitatory mechanisms can dictate the duration of pain (McGreevy et al., 2011), making it a relevant target for treatment.

Mechanisms of neuroinflammation

Inflammation is a natural response that systematically occurs following tissue or nerve damage and is essential for restoring homeostasis (Ellis & Bennett, 2013; Pape et al., 2010). However, in various chronic pain conditions that originate from a peripheral insult, the restoration process of inflammation following lesion is altered resulting in an excessive and prolonged inflammation (Schinkel et al., 2006). This physiological reaction subsequently triggers a complex cascade of events eventually leading to neuroinflammation and pain chronification (Scholz & Woolf, 2007; Walker, Kavelaars, Heijnen, & Dantzer, 2014; Watkins, Milligan, & Maier, 2003). Persistent inflammation that originates from the injured-body region and later invades the CNS significantly alters the blood-brain barrier's (BBB) permeability, allowing undesired materials to reach the brain, compromising its ability to promote brain equilibrium (DosSantos, Holanda-Afonso, Lima, DaSilva, & Moura-Neto, 2014; Huber et al., 2001; Varatharaj & Galea, 2017). Disruption of the BBB's permeability also occurs following a brain insult (traumatic brain injury), where excessive inflammatory response disrupts and crosses the BBB to initiate a systemic immune response (Rowe et al., 2016). BBB leakage facilitates inflammatory spreading in regions that are otherwise not related to the initial injury, which can ultimately result in hyperalgesia (Rowe et al., 2016). It is interesting to note that this inflammatory response may become increasingly detrimental when patients suffer from multiple injuries, such as a brain insult combined with an orthopaedic trauma, where inflammatory response from each injury

exacerbates its diffusion throughout the brain (Rowe et al., 2016). Health-care professionals should be aware of this reality, especially since patients with acquired traumatic injuries often suffer from multiple injuries (Gross, Schuepp, Attenberger, Pargger, & Amsler, 2012; Jodoin et al., 2016).

When looking at chronic pain mechanisms, one realizes the obvious interaction existing between the nervous system and the immune system, where persistent inflammatory response and central sensitization mutually influence each other's development (Franco, Pacheco, Lluis, Ahern, & O'Connell, 2007; Grace, Hutchinson, Maier, & Watkins, 2014; Ji, Xu, & Gao, 2014). Indeed, inflammatory response can modulate central sensitization by facilitating glutamatergic transmission while decreasing GABAergic transmission (Bleakman, Alt, & Nisenbaum, 2006; Crowley, Cryan, Downer, & O'Leary, 2016; Haroon et al., 2016). A study conducted by Latremoliere and Woolf (2009) suggested that glial cells malfunction and neuroinflammation are core contributing factors of central sensitization. Microglia, a glial cell typically responsible for removing neurotoxins in cases of injury or infection such as bacteria, scavenge cellular debris, and foreign invaders, may become unable to successfully fulfill its role, thereby worsening inflammation (Chen & Trapp, 2016; Ellis & Bennett, 2013). Indeed, upregulated microglial activation provokes a cascade of events where inflammatory processes are activated by recruiting other glial cells such as astrocytes (slower onset that may be responsible for the maintenance of pain states) and oligodendrocytes and by facilitating the neuronal release of glutamate and neurotoxins (Rock et al., 2004; Watkins, Milligan, & Maier, 2001). Schwann cells, another type of glial cells, also facilitate inflammatory processes by secreting pro-inflammatory cytokines (Campana, 2007) and reducing anti-inflammatory cytokines (J. M. Zhang & An, 2007). This cascade of event coincides with a shift from pro-inhibitory to pro-facilitatory cytokines (Vanegas & Schaible, 2004). Pro-inflammatory cytokines, such as tumor necrosis factor (TNF), Interleukin 6 (IL-6) and Interleukin-1 beta (IL-1b), are considered glial mediators that induce a metabolic cascade promoting excessive release of glutamatergic neurotransmission and GABAergic down-regulation (Galic, Riazi, & Pittman, 2012; Watkins et al., 2003; Zhang & An, 2007). The ensuing state of disinhibition and hypersensitivity was found to mediate pain habituation processes (Crowley et al., 2016; Davis & Moayedi, 2013; DeLeo, Tanga, & Tawfik,

2004; Gwak, Crown, Unabia, & Hulsebosch, 2008; Hamilton & Attwell, 2010; Kawasaki, Zhang, Cheng, & Ji, 2008). Through their central role on the development and persistence of inflammatory responses, central sensitization and glutamate upregulation, high concentrations of pro-inflammatory cytokines within the CNS lead to hypersensitivity and long-term plasticity changes (Baron et al., 2010; DeLeo et al., 2004; Milligan & Watkins, 2009; Moalem & Tracey, 2006; Ye et al., 2013). This interaction between the nervous system and the immune system is further supported by studies in TBI patients showing that excessive glutamate production promotes inflammatory response and enables immune cells to enter the brain due to BBB breakdown (Das, Mohapatra, & Mohapatra, 2012). BBB breakdown occurs as a secondary injury that can last days to weeks along with multiple other physiopathological reactions such as, but not limited to, excitotoxicity due to excessive glutamate release and inflammation (Choi, 1987; Greve & Zink, 2009).

Under homeostasis conditions, the GABAergic system exerts immunoprotective effects by suppressing pro-inflammatory cytokines (Bhat et al., 2010; Prud'homme et al., 2013; Walker et al., 2014). In chronic pain, however, downregulated GABA inhibition occurs in a context of pro-inflammatory cytokine excessive release, which further contributes to neuroinflammation (Crowley et al., 2016). Lastly, studies conducted at the brain level showed that neuroinflammation impacts neuronal connectivity (maladaptive plasticity) and disrupts CNS homeostasis in the pain matrix. Indeed, these regions were characterized by glial cell and cytokine overproduction (Di Filippo, Sarchielli, Picconi, & Calabresi, 2008; Loggia et al., 2015). More importantly, Loggia et al. (2015) found that glial cell activation offered a pattern within S1, M1 and the thalamus that coincides with somatotopic representation of affected body part. A possible explanation for this phenomenon is the effects of neuroinflammation on BDNF expression, such that excessive pro-inflammatory cytokines alter and change BDNF expression, which later results in maladaptive plasticity (Calabrese et al., 2014).

Repetitive TMS

Repetitive TMS is a non-invasive neuromodulation technique that recently gained in popularity as a potential alternative intervention for treating various pain conditions (Galhardoni et al., 2015; Lefaucheur et al., 2006; Platz, 2016). This procedure allows to directly modulate cortical activity through the induction of repetitive magnetic field pulses that vary according to various parameters, namely the number of stimuli, the strength of the stimuli, the duration of the stimuli, the length of the interval between stimuli, and the targeted area of the brain (Wassermann, 1998). This technique differs from traditional TMS by its ability to deliver repetitive pulses at regular intervals, as opposed to single pulses, that have long-lasting effects (Wassermann, 1998). Repetitive TMS was first introduced within the medical field for its therapeutic effects on major depression (George et al., 1995), which offered a novel alternative to drug-resistant patients (Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson, 2012). This technique is approved by the U.S. Food and Drug Administration (FDA) since 2008 for its well-demonstrated efficacy in major depression patients at reversing deficient hypoactive cortical excitability in a region that is key to mood regulation and emotion responsiveness, the dorsolateral prefrontal cortex (DLPFC) (Baeken & De Raedt, 2011; George et al., 2010; Pascual-Leone, Rubio, Pallardo, & Catala, 1996). More recently, this technique has shown promising results in treating other pathologies such as, but not limited to, schizophrenia, pain conditions, epilepsy, and Parkinson's disease (Bae et al., 2007; Chou, Turner et al., 2015; Chou, Hickey et al., 2015; Galhardoni et al., 2015; Prikryl, 2011; Zhang et al., 2013).

Accumulating evidence suggests that rTMS could induce short and long-term analgesic effects in various chronic pain conditions (CRPS, neuropathic pain, low back pain, phantom limb syndrome, fibromyalgia) (Andre-Obadia et al., 2006; Canavero et al., 2002; Khedr et al., 2005; Lefaucheur, 2006; Lefaucheur et al., 2014; Pleger et al., 2004), which can last beyond the duration of the stimulation and are free of adverse side effects (Lefaucheur et al., 2014; Platz, 2016), with the exception of possible transient headaches in a minority of patients (Klein et al., 2015). The success of rTMS in treating chronic pain states stems from its ability to precisely modulate and restore the main markers of brain plasticity, namely LTP and LTD but its clinical applicability remains debated (Bliss & Cooke, 2011). Baron (2006) suggested that therapies able to modulate these two mechanisms (LTP and LTD) within the descending pathways show promise in treating pain

conditions. Moreover, afferent nociceptive transmission can be reduced by the CNS through the descending or modulatory system (Voscopoulos & Lema, 2010). In this regard, rTMS appears particularly suitable in patients suffering from a peripheral insult (fracture) for its ability to precisely stimulate the corresponding brain region of the affected body region, therefore offering a precise and well-tailored therapeutic alternative. In other words, rTMS could be applied specifically on the somatotopic representation of the injured dermatome within M1 (Eisenberg et al., 2005). Moreover, we believe that this technique is highly suitable and polyvalent for treating pain conditions as it successfully targets, directly or indirectly, specific mechanisms that various acquired traumatic injury patients share, namely central sensitization and neuroinflammation: a major advantage over current pharmacological treatments of pain. The following section will describe how rTMS may help in treating acute pain early on by modulating central sensitization and neuroinflammatory mechanisms of pain.

Repetitive TMS and central sensitization

Given that pain conditions are characterized by early installation of maladaptive plasticity processes, it would appear logical to implement pain relief interventions that directly target plasticity mechanisms (McGreevy et al., 2011; Nijs et al., 2015; Pelletier, Higgins, & Bourbonnais, 2015). Accordingly, rTMS is specifically used to modulate and restore synaptic plasticity equilibrium in the brain through the induction of electromagnetic fields, whether aiming for LTP or LTD effects over the targeted brain area (Pashut et al., 2011). Given that the ultimate goal is to optimize the function of brain structures implicated in pain perception and to reduce pain, rTMS appears as an intervention of choice in efficiently restoring unbalanced excitatory and inhibitory systems. This is further supported by a recent study published by Clauw (2015) suggesting that pain therapies that allow to block excitatory and increase inhibitory neurotransmitters involved in pain states should logically yield positive results. More specifically, in a context of acute pain where cortical facilitation predominates, low-frequency rTMS and TMS-based theta-burst stimulation were shown efficient in inducing GABA-mediated inhibitory effects (Stagg et al., 2009; Trippe, Mix, Aydin-Abidin, Funke, & Benali, 2009). Of note, theta-burst stimulation (TBS) is a more novel technique that offers the possibility of delivering a

significantly higher number of stimulation bursts within a shorter period of time (< 2 min) when compared to conventional rTMS protocols (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). In particular, a magnetic resonance spectroscopy study by Stagg et al. (2009) showed that continuous TBS (c-TBS) over M1, a type of TBS protocol that reduces cortical motor excitability, significantly increased GABA concentration in the stimulated cortical region, relative to the unstimulated control site (Huang et al., 2005). Increased GABA concentration in M1 following c-TBS should therefore reduce the excessive cortical pain network activation in addition to help the GABA system regain its neuroprotective function. Indeed, GABA plays a major role in reducing pain levels (analgesia) in the brain but also throughout the descending pathway (Crowley et al., 2016; Jasmin, Rabkin, Granato, Boudah, & Ohara, 2003; Moisset, de Andrade, & Bouhassira, 2016; Nardone et al., 2016), suggesting that a restoration of the deficient neuronal plasticity would be beneficial. In parallel, as previously discussed, NMDA receptors play an important role in the development and perpetuation of chronic pain (Ultenius et al., 2006). Indeed, studies showed that rTMS inhibitory effects could effectively block NMDA receptors activity, thus preventing further LTP induction and maintaining brain equilibrium (Chervyakov, Chernyavsky, Sinitsyn, & Piradov, 2015; Naro et al., 2016).

Another distinctive asset of rTMS is that it can modify brain activity in regions connecting with the stimulated region, such as M1 (Passard et al., 2007). Indeed, rTMS effects expand beyond the stimulated region to multiple cortical (cingulate, orbitofrontal and prefrontal cortices, thalamus, and striatum) and subcortical (periaqueductal gray matter) regions of the pain matrix (Marlow, Bonilha, & Short, 2013; Mylius, Borckardt, & Lefaucheur, 2012; Naro et al., 2016) through shared connections between M1 and the thalamus (Holsapple, Preston, & Strick, 1991), the latter structure acting as a relay station to numerous brain regions that contribute to neuronal activity modulation. Furthermore, maladaptive plasticity and central sensitization also occur in spinal cord descending pathways (Vanegas & Schaible, 2004), which play an important role in central sensitization. The spinal cord represents the crossroad between the peripheral, where the injury occurred in a context of musculoskeletal injuries, and the central nervous system, where rTMS effects on excitatory/inhibitory mechanisms take place. Indeed, persistent pain is associated with sustained functional abnormalities of the descending corticospinal pathway

through a progressive reinforcement of excitatory mechanisms (Millan, 2002). In pain-inducing conditions, descending inhibitory mechanisms should therefore be enhanced in order to effectively and rapidly reinstate LTP and LTD balance (Millan, 2002). Given the long-term relief of depressive symptoms (George et al., 1995; Lee et al., 2012) with rTMS, one could make use of inhibition-inducing rTMS protocols to reverse the excitatory state set off by pain-inducing peripheral injury via lasting desensitization from the CNS to the injury site. Interestingly, rTMS could presumably target the origin of nociception (peripheral terminal) itself by projecting through the dorsal horn of the spinal cord where takes place most of the pain sensitization processes.

Repetitive TMS and Neuroinflammation

To our knowledge, there has been very few studies, if any, that looked specifically at the potential effects of rTMS on neuroinflammation in patients with acquired traumatic injuries. This is surprising considering that glial cells are known to respond to electrical activity in various ways, highlighting the potential relevance of rTMS application in the treatment of pain (Cullen & Young, 2016). In a recent TBI rodent model, rTMS successfully reduced neuroinflammation by modulating astrocytes and microglia activity (Sasso et al., 2016), both important markers of pain chronification. Moreover, microglia and astrocytes can respectively up-regulate CNS excitability and modulate synaptic plasticity (Cullen & Young, 2016). This is further supported by a recent study by Loggia et al. (2015) that showed an increase in activation of glial cells in specific brain regions, namely S1, M1, and the thalamus that corresponded to somatotopic representation of the affected limb. This is particularly interesting knowing that rTMS can precisely modify activity in these regions and that glial cells respond to electrical current (Cullen & Young, 2016). It would therefore stand to reason that durable inhibitory effects of multisession rTMS regimens could also help reduce immune system activity by reducing otherwise hyperactive glial cells.

Considering the association between the immune system and the CNS (Franco et al., 2007; Grace et al., 2014; Ji et al., 2014), it is expected that a reduction in central sensitization could positively

impact neuroinflammation. In parallel, accumulating evidence suggests that upregulated GABA neurotransmitter release can control excitoxicity and ultimately reduce neuroinflammation (Crowley et al., 2016). This is further supported by pharmacological studies showing the efficacy of drugs targeting GABA receptors in reducing neuroinflammation (Rudolph & Mohler, 2006). These findings raise the possibility that a restoration of the GABAergic modulator system via rTMS could help reduce neuroinflammation. A recent study provided evidence of a link between excessive glutamatergic system activity and BBB's permeability through overactivation of NMDA receptors (Vazana et al., 2016). Indeed, it has been shown that increased levels of glutamate availability directly affect BBB's integrity and increases intracellular calcium levels, which further compromises BBB integrity and central sensitization (Coderre & Melzack, 1992; Vazana et al., 2016). This suggests that if BBB's permeability could be restored with rTMS by downregulating NMDA receptor activity, inflammatory spreading could be restrained (DosSantos, Ferreira, Toback, Carvalho, & DaSilva, 2016). This is particularly interesting in a context of acquired traumatic injuries where either peripheral insults (fractures) or central insults (traumatic brain injuries) induces acute disruptions of BBB permeability, which in turn promotes spreading of inflammatory response (Adelson, Whalen, Kochanek, Robichaud, & Carlos, 1998; Huber et al., 2001; Price, Wilson, & Grant, 2016).

In addition to potential rTMS suppressing effects on glutamatergic activity through the induction of GABA-like activity, recent rTMS study conducted in rodent models of stroke showed that rTMS can down-regulate the expression of TNF (Ljubisavljevic et al., 2015), an important pro-inflammatory cytokine. Taken together, the use of rTMS could be effective in breaking down the inflammatory cascade of events by increasing the level of anti-inflammatory cytokines and by preventing the inflammatory response to invade the spinal cord.

M1 should be the targeted region for stimulation

Multiples studies have investigated the efficacy of rTMS associated with the stimulation of various cortical sites (M1, M2, DLPFC, S1, S2, supplementary and premotor areas) to determine which cortical area provides optimal analgesia (Hirayama et al., 2006; Sasso et al., 2016; Treister, Lang,

Klein, & Oaklander, 2013). Although the exact underlying mechanisms are not well understood, accumulating evidence show that M1 is a target of choice in intervening against pain (Antal & Paulus, 2010; DosSantos et al., 2016; Hirayama et al., 2006; Treister et al., 2013). Multiple explanations can be proposed but warrant precautions as robust and replicated evidence is still lacking. A potential explanation for this phenomenon emerges from the anatomical connections between M1 and the thalamus (Holsapple et al., 1991; Moisset et al., 2016; Moisset et al., 2015), a brain structure that acts as a relay station with regions involved in the "pain matrix", as well as its connection with regions that are involved in pain processing (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Moisset et al., 2016; Moisset et al., 2015; Peyron, Laurent, & Garcia-Larrea, 2000). Furthermore, M1 directly projects through descending pathways where sensory-discriminative components of pain are located (Lefaucheur et al., 2006). Indeed, M1, a region rich in NMDA receptors, is the primary entrance to the corticospinal descending pathway (Rossini et al., 2015) and changes in its excitability (LTP and LTD) can easily be measured in humans. Studies show that rTMS can modulate descending pathway activity by reaching antinociceptive mechanisms through M1. Interestingly, afferent nociceptive transmission can also be reduced by the CNS through the descending or modulatory system (Voscopoulos & Lema, 2010). Modulation of antinociceptive mechanisms via M1 stimulation could therefore act on both sensory discriminative features of pain as well as emotional and affective motivation processing of pain (Lefaucheur, 2004; Lefaucheur, Drouot, Menard-Lefaucheur, Zerah, et al., 2004; Passard et al., 2007). Moreover, there is convincing evidence suggesting that pain may lead to significant memory impairments in traumatically injured patients due, in part, to the shared connections between the pain matrix and the hippocampus (Moriarty, McGuire, & Finn, 2011). Although it may be speculated that low frequency rTMS could conceptually worsen memory alterations through its downregulating effects on LTP, we believe that restoring normal brain activity with rTMS through pain reduction effects would in fact positively affect memory function.

Furthermore, rTMS is a dose-dependent pain treatment for which the efficacy varies according to the stimulation frequency, the number of intervention sessions and stimulations, and the type of stimulation (Lefaucheur et al., 2014). Maintenance therapy or boost sessions, where patients

later return to the clinic for sporadic treatment sessions following one or two weeks of consecutive rTMS treatment, show prolonged benefits of rTMS-induced analgesic effects that can last 6 months to a year (Galhardoni et al., 2015; Lefaucheur, 2004; Lefaucheur, Drouot, Menard-Lefaucheur, & Nguyen, 2004; Mhalla et al., 2011). As proposed in a recent review by Galhardoni et al. (2015), the implementation of boost sessions appears fundamental in prolonging the effects of non-invasive brain stimulation-based interventions on both the level of pain and the emotional aspects of pain. Furthermore, as suggested by Lefaucheur et al. (2014), increasing the number of pulses delivered through additional treatments sessions should lead to prolonged rTMS-induced analgesia. TBS, a more novel technique, offers the possibility of delivering a significantly higher number of stimulation bursts within a shorter period of time (< 2 min). Preliminary results suggest that TBS is more effective than conventional rTMS in treating chronic pain stages (Huang et al., 2005; Moisset et al., 2016; Moisset et al., 2015). More specifically, prolonged-continuous TBS (pcTBS) applied over M1, a type of stimulation protocol aiming to restore normal intracortical excitability and to reduce synaptic activity, was recently shown more effective than other TMS-based pain relief protocols in treating both acute and chronic pain states (Antal & Paulus, 2010; Moisset et al., 2016; Moisset et al., 2015). Future studies contrasting the efficacy of available TMS intervention options with larger samples consisting of diverse pain-inducing pathologies are needed to optimize TMS-based intervention protocols. At this point, it would be premature for rTMS to completely replace the use of pharmacological therapy or any other pain-relief strategy, but future studies should investigate whether the combination of rTMS with other therapeutic approaches could reduce the use of pain relief drugs (Mills, Torrance, & Smith, 2016; Picarelli et al., 2010). Moreover, it is to note that multidisciplinary, biopsychosocial rehabilitation (orthopaedic care, physical therapy, psychological therapy, pharmacological therapy, occupational therapy, massage therapy, etc.) was shown effective in treating patients afflicted with chronic pain (Guzman et al., 2001; Scascighini, Toma, Dober-Spielmann, & Sprott, 2008; Volker et al., 2017) but its applicability during the acute phase remains debated (Cochrane et al., 2017). Consequently, it would be of great interest to evaluate the impact of acute rTMS intervention in reducing the financial burden associated with chronic pain management.

Patients should be treated early on to prevent pain chronification

For obvious reasons, focus should be put on preventing rather than treating chronic pain. In this regard, treatment timing appears particularly important, given that there is a critical time window for optimal pain recovery. Indeed, as reported by Vranceanu et al. (2016), patients who have been absent from work for < 12 weeks are more likely to return to work compared to patients who took longer. This is particularly alarming considering that pain becomes chronic after 12 weeks and that a wide proportion of patients who suffer from chronic pain are in fact within the working-age range (Rustoen et al., 2005). For these reasons, we stress the importance of beginning the rTMS intervention as early as possible.

If we then focus on the underlying mechanisms of pain, it also makes sense to intervene rapidly in order to prevent acute pain from transitioning into chronic pain, given that neuroinflammatory response spreads diffusely throughout the brain in chronic pain. As discussed earlier, during the transitioning from the acute to the chronic pain stage, changes in the brain occur rapidly following injury (Moseley & Flor, 2012), where nociceptive inputs no longer originate solely from the injured body site but recruit otherwise healthy areas located near the inflammation site. This leads pain-facilitating networks to become well anchored within the brain, where not only the sensory-discriminative features of pain are involved, as it is the case in acute pain, but also the affective-motivational processing (Doan, Manders, & Wang, 2015; Hashmi et al., 2013). This can partly explain the association between chronic pain and multiple comorbidities such as anxiety, depression, and social isolation (McWilliams, Cox, & Enns, 2003), which makes it even more difficult to treat due to the convergence of multiple and complex mechanisms.

It also appears logical that rTMS could provide optimal results in treating acute pain following a musculoskeletal injury, as opposed to chronic pain, for its more direct effects on targeting a specific body region in acute pain as opposed to when chronic pain effects have spread throughout the brain (Bruehl, 2015; Katz & Seltzer, 2009). This is further supported by recent work by Bliss and Cooke (2011) suggesting that low-frequency, GABA-agonist rTMS stimulation provide optimal results in reversing LTP-like mechanisms if treated rapidly following the accident. The proposed inhibition-enhancing rTMS intervention in acute pain contrasts sharply with most rTMS and chronic pain studies showing more promising results when using high-frequency rTMS

protocols (Galhardoni et al., 2015). This discrepancy in treatment approaches when initiated in the acute as opposed to the chronic phase is in line with significant physiopathological differences existing between acute and chronic pain states (Fornasari, 2012; Phillips & Clauw, 2011; Vellucci, 2012). In acute pain, the CNS is in an excitatory state via the "wind-up" phenomenon where no endogenous compensatory mechanisms have been put in place within the spinal cord or the brain (central sensitization and maladaptive plasticity). Accordingly, rTMS may reveal to be less effective in relieving pain symptoms in chronic pain states such as fibromyalgia given that pain origin cannot easily be defined (Staud & Rodriguez, 2006). Nevertheless, multiple studies have provided positive effects of rTMS in treating fibromyalgia with an effect on overall pain levels, quality of life and mood (Boyer et al., 2014; Knijnik et al., 2016; Mhalla et al., 2011). In the context of acute pain and based on the physiological mechanisms discussed in this review, low frequency rTMS should be applied during the early stages of pain in an attempt to suppress excitotoxic activity and inflammation as well as to restore GABAergic activity to normal value. This would ultimately allow increasing synaptic strength to prevent lowering of the firing threshold, and thereby decreasing the risk of diffuse maladaptive plasticity.

Furthermore, regions involved in acute pain, namely S1, S2 and the thalamus, share more direct connections with M1 than regions activated in chronic pain (anterior cingulate cortex, insular cortex, prefrontal cortex, amygdala) (Davis & Moayedi, 2013; Yen & Lu, 2013). By increasing the availability of inhibitory GABAergic neurons through rTMS, the cascade of maladaptive inflammation and sensitization (excitatory neurons) could potentially be blocked from crossing the BBB and reaching the brain, thereby preserving brain homeostasis. This is further supported by studies showing that "wind-up" and peripheral sensitization can be attenuated by blocking the activity of NMDA receptors and increasing GABA-like activity (Herrero et al., 2000), two phenomena that can be achieved via rTMS. Ultimately, this could not only reduce physical suffering but it may also lessen the risk of psychological distress (Pergolizzi et al., 2013).

Conclusion

Chronic pain has deleterious effects on the quality of life of patients and generates important costs. For this reason, many efforts have been devoted in developing treatments that will allow patients to rapidly return to their previous level of functioning. Pharmacological treatment remains, to this day, the therapy of choice despite important shortcomings and serious adverse effects. For this reason, alternative treatments have gained increasing popularity in an attempt to reduce, and ultimately replace, the use of pharmacological treatments. Repetitive TMS appears particularly suitable for its ability to modulate synaptic plasticity, a phenomenon greatly altered in the early stages of pain chronification. This review presents evidence that rTMS can act on key mechanisms of pain, namely central sensitization and neuroinflammation, by reducing excitatory activity through the induction of GABA-like activity. Current data suggest that optimal results can be achieved by stimulating M1 for its direct connection with the descending pathway of the spinal cord and its ability to precisely target the somatotopic region of the affected limb and therefore reach the nociceptor peripheral terminal. From a mechanistic perspective, current knowledge about chronic pain and action mechanisms of rTMS supports the importance of applying inhibitory rTMS interventions as early as possible to prevent the transition from acute to chronic pain in patients with acquired traumatic injuries. More studies are needed to characterize the effects of rTMS on neuroinflammation in pain chronification but also to optimize treatment modalities.

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Article 6: Moderate to severe acute pain disturbs motor cortex intracortical inhibition and facilitation in orthopedic trauma patients: A TMS study

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Abstract

Objective: Primary motor (M1) cortical excitability alterations are involved in the development and maintenance of chronic pain. Less is known about M1-cortical excitability implications in the acute phase of an orthopedic trauma. This study aims to assess acute M1-cortical excitability in patients with an isolated upper limb fracture (IULF) in relation to pain intensity.

Methods: Eighty-four (56 IULF patients <14 days post-trauma and 28 healthy controls). IULF patients were divided into two subgroups according to pain intensity (mild versus moderate to severe pain). A single transcranial magnetic stimulation (TMS) session was performed over M1 to compare groups on resting motor threshold (rMT), short-intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval cortical inhibition (LICI).

Results: Reduced SICI and ICF were found in IULF patients with moderate to severe pain, whereas mild pain was not associated with M1 alterations. Age, sex, and time since the accident had no influence on TMS measures.

Discussion: These findings show altered M1 in the context of acute moderate to severe pain, suggesting early signs of altered GABAergic inhibitory and glutamatergic facilitatory activities.

Introduction

Orthopedic trauma (OT) patients are routinely afflicted by pain and it is considered the most common and debilitating symptom reported among this population (Albrecht et al., 2013; Archer, Castillo, Wegener, Abraham, & Obremskey, 2012). Optimal pain control is an OT care priority as pain interferes with trauma recovery and affects outcome (Castillo et al., 2017; Velmahos et al., 2019).

A growing body of research is currently focused on developing alternative pain management techniques to tackle the alarming drawbacks associated with current standards of care. Among these alternatives, transcranial magnetic stimulation (TMS) has gained attention in recent years for its dual role: 1) its ability to objectively assess pain mechanisms; and 2) its potential applicability in pain management. In chronic pain studies, the primary motor cortex (M1) commonly serves as the targeted brain region due to its connections with the nociceptive system and the known effect of pain on motor function (Frot, Magnin, Mauguiere, & Garcia-Larrea, 2013; Martucci & Mackey, 2018). Despite some variability across TMS studies, there is extensive evidence of an altered balance between inhibitory and facilitatory circuits of M1 in various chronic pain conditions (i.e. fibromyalgia, neuropathic pain, complex regional pain syndrome, phantom limb pain, chronic orofacial pain) (Parker, Lewis, Rice, & McNair, 2016; Woolf, 2011). These results highlight maladaptive plasticity within the motor system. M1-cortical excitability alterations have been associated with the severity of the clinical symptoms such as pain intensity, hyperalgesia, and allodynia (Pfannmoller, Strauss, Langner, Usichenko, & Lotze, 2019; Schwenkreis et al., 2010), pointing to the value of TMS as an objective tool that reflects functional alterations. Moreover, cortical excitability restoration through repetitive TMS (rTMS), a technique known to induce lasting modulation effects on brain activity through a multiple day session paradigm, has shown some efficacy in reducing the magnitude of pain, even in refractory chronic pain patients (Gaertner et al., 2018; Herrero Babiloni, Guay, Nixdorf, de Beaumont, & Lavigne, 2018; Lefaucheur, Drouot, Menard-Lefaucheur, Keravel, & Nguyen, 2006; Lima & Fregni, 2008; O'Connell, Wand, McAuley, Marston, & Moseley, 2013; Picarelli et al., 2010). Overall, these

results support the role of cortical excitability on pain intensity in chronic pain patients and the potential clinical utility of TMS in pain management among this population.

On the other hand, acute pain initiated by an OT, such as following a fracture, has received little to no attention, despite being highly prevalent. With 15% to 20% of all physician visits intended to address pain-related issues (Koleva, Krulichova, Bertolini, Caimi, & Garattini, 2005; Mantyselka et al., 2001), management of acute pain following OT still remains medically challenging (Alves et al., 2016; Chou et al., 2016; Lynch, 2011; Meissner et al., 2018). Knowing that acute and chronic pain belong to the same continuum and that there is clear evidence of success in the use of rTMS in treating chronic pain, this technique could serve as a potential treatment tool in the early phase of fracture pain by tackling key elements of pain chronification. First, however, a better understanding of the involvement of M1-cortical excitability in acute pain is necessary.

From a physiological point of view, it remains unclear whether motor cortical excitability impairments are expected in a context of acute pain following an OT. On one hand, neuroimaging studies suggest that possible disturbances within M1 only arise once chronic pain has developed, with acute and chronic pain exhibiting distinct and non-overlapping brain activation patterns (Baliki et al., 2012; Chang et al., 2018; Hashmi et al., 2013; Mansour, Farmer, Baliki, & Apkarian, 2014; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). On the other hand, there is evidence supporting alterations of M1-cortical excitability during acute pain states. Indeed, Voscopoulos and Lema highlight early neuroplasticity involvement of GABA inhibitory interneurons following a peripheral insult, which may contribute to later transition to chronic pain (Voscopoulos & Lema, 2010). In parallel, Pelletier and colleagues (Pelletier, Higgins, & Bourbonnais, 2017) suggested that pain intensity may act as the driving factor leading to M1-cortical excitability alterations rather than the state of chronic pain itself. This assumption was made by authors after obtaining similar M1 deficiency patterns across chronic pain conditions of various origins. Other TMS studies also showed that pain of moderate to severe intensity (score $\geq$4 on numerical rating scale (NRS)) leads to greater motor cortex impairments (Schwenkreis et al., 2010). The relationship between pain intensity in the acute state and its impact on cortical excitability parameters appears a relevant target of investigation.

So far, very few studies have looked into the association between acute pain and M1-cortical excitability. These studies have mainly focused on experimental pain models in healthy subjects. In parallel, rTMS studies have been shown effective in both alleviating acute experimental pain and modulating alterations in M1-cortical excitability (Leo & Latif, 2007; Tamura et al., 2004). Taken together, these findings show that M1 alterations can occur in the context of acute pain and that rTMS over M1 can successfully modulate nociceptive afferent information and restore M1 alterations, even for transient pain sensation in healthy controls. However, due to the subjective nature of pain sensation along with intrinsic differences in pain characteristics across conditions and individuals, translation between experimental pain model and clinical pain following an OT is limited. Therefore, if we are to consider the potential clinical utility of rTMS in alleviating acute pain, studies need to be conducted in a clinical population.

This study therefore aims to assess acute M1-cortical excitability functioning through well-established TMS paradigms according to pain intensity in patients who are in the acute pain phase following an isolated upper limb fracture (IULF). We hypothesize that M1-cortical excitability alterations will be found in patients with higher levels of pain compared to healthy controls and to IULF patients with mild pain.

Materials and Methods

This work was approved by the Hôpital du Sacré-Coeur de Montréal' Ethics Committee (Approval number: 2017-1328). A written consent was obtained by all participating subjects prior to the start of the study. A financial compensation was given to all subjects for their participation.

Participants

Our sample included 1) patients who have suffered from an isolated upper limb fracture (IULF) and 2) healthy controls. Patients with an IULF were initially recruited from various orthopedic clinics affiliated to a Level 1 Trauma Hospital. To be included in the study, patients had to be aged between 18 and 60 years old and have sustained an IULF (one fractured bone from upper body extremities) within 14 days post-injury. Recruitment of IULF patients took place on the day of the first medical appointment at the orthopedic trauma clinic with the orthopedic surgeon. Testing

was conducted within 24 hours post-medical consultation. All testing measures had to be completed prior to surgical procedures (if any) given the known impact of surgery on increased inflammatory response and pain perception (Pogatzki-Zahn, Segelcke, & Schug, 2017). Exclusion criteria consisted of a history of traumatic brain injuries, a diagnosis of and/or a treatment for a psychiatric condition in the last ten years, musculoskeletal deficits, neurological conditions (i.e. epilepsy), chronic conditions (cancer, uncontrolled diabetes, cardiovascular illness, high blood pressure), the use of central nervous system-active medication (hypnotics, antipsychotics, antidepressant, acetylcholinesterase inhibitor, anticonvulsant), history of alcohol and/or substance abuse, acute medical complications (concomitant traumatic brain injury, neurological damage, etc.), and being intoxicated at the time of the accident and/or at the emergency visit. Of note, IULF patients were not restrained from using analgesic medication (acetaminophen, ibuprofen, opioids, etc.) during testing to assure comfort and to avoid interfering with pain management.

The control group consisted of healthy right-handed adults recruited through various social media platforms. As per usual practice in conducting M1 TMS studies, only right-handed control participants were selected as stimulation over non-dominant M1 has been associated with accentuated within-subject variability (Civardi, Cavalli, Naldi, Varrasi, & Cantello, 2000; Hammond, Faulkner, Byrnes, Mastaglia, & Thickbroom, 2004). They self-reported to be free of all previously mentioned exclusion criteria.

Study participants were also screened for TMS tolerability and safety (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009).

Assessment measures

Total assessment procedures (including consent) were conducted over a single, 90-minute session. First, participants were invited to complete self-administered questionnaires to gather demographic information and clinical outcome measures (pain intensity and functional disability indices). More specifically, demographic data such as age, sex, and level of education were documented and used to ensure homogeneity between groups.

Clinical outcome: Pain intensity and functional disability indices

To assess the perceived level of pain at the time of testing, the numerical rating scale (NRS), a routinely used standardized generic unidimensional clinical pain questionnaire, was administered (Downie et al., 1978; Williamson & Hoggart, 2005). To complete the NRS, participants had to circle a number that best fit their current level of pain on the 11-point pain intensity scale, with numbers ranging from 0 ("no pain") to 10 ("worst possible pain"). In order to test the hypothesized impact of acute pain intensity on M1 cortical excitability, IULF patients were divided into two distinct groups according to NRS score: 1) IULF patients who self-reported moderate to severe pain intensity (NRS $\geq$4 out of 10); 2) IULF patients with mild pain intensity (NRS <4). The cut-off pain intensity scores are based on previous pain studies (Gerbershagen, Rothaug, Kalkman, & Meissner, 2011; Schwenkreis et al., 2010; Zelman, Gore, Dukes, Tai, & Brandenburg, 2005).

The disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire was used as a tool to assess an individual's ability to perform common specific everyday activities relying on upper extremity limbs (Angst, Schwyzer, Aeschlimann, Simmen, & Goldhahn, 2011; Gummesson, Atroshi, & Ekdahl, 2003). This questionnaire consists of 30 items, including 6 that are symptom-related and 24 that are function-related, where patients were asked to rate the level of disability on each activity as experienced since their accident. Continuum of scores on this questionnaire varies between 0 (no disability) and 100 (extreme difficulty).

Comprehensive assessment of M1 cortical excitability using TMS.

To assess M1 cortical excitability, a TMS figure-of-eight stimulation coil (80mm wing diameter), attached to a Bistim^2 Magstim transcranial magnetic stimulators (*Magstim Company*, Whitland, Dyfed, UK), was used. The TMS-coil was positioned flat on the scalp over M1 at a 45° angle from the mid-sagittal line, with its handle pointing backwards. In the IULF group, the TMS coil was positioned over M1 contralaterally to the injury, whereas in the control group, the TMS-coil was systematically positioned over the dominant left hemisphere. Motor evoked potentials (MEP) recordings from the abductor pollicis brevis (APB) was performed using three electrodes positioned over the belly of the target muscle (active electrode (+)), between the distal and proximal interphalangeal joints of the index (reference (-)), and on the forearm (ground). Optimal stimulation site was determined based on the coil position which evoked highest peak-to-peak

MEP amplitudes from the target muscle. We used a 3D tracking system (Northern Digital Instruments, Waterloo, Canada) to ensure accurate and consistent TMS coil positioning on the targeted site.

Various well-established TMS protocols were conducted to investigate M1 excitatory and inhibitory mechanisms using single and paired-pulse paradigms. Single pulse magnetic stimulations were first used to establish the resting motor threshold (rMT), i.e. the minimal stimulation intensity needed to elicit a MEP of at least 0.05mV in five out of ten trials (Rossini et al., 2015). An interstimulus interval, varying from 8 to 10 seconds, was applied to control for possible residual effects of TMS stimulation on M1 activity (Chen et al., 1997). The sequence of stimulation intensity was randomly generated by a computer. Short intra-cortical-inhibition (SICI) and facilitation (ICF) were measured via a classic paired-pulse paradigm (Kujirai et al., 1993; Ziemann, Rothwell, & Ridding, 1996). The latter protocol involves the application of two successive TMS pulses, the first pulse set at 80% of the rMT intensity (subthreshold; conditioning stimulus) and the second pulse set at 120% of the rMT (suprathreshold; test stimulus) separated by an interstimulus interval (ISI) of a predetermined duration (Kujirai et al., 1993). To test for SICI, a measure attributed to $GABA_A$ interneurons and receptors activity (Ziemann, 2003), one sequence of 10 paired-pulse stimulations was completed with an ISI set at 3ms. To test for ICF, one sequence of 10 stimulations was performed with ISI set at 12ms. Measure of ICF is thought to be mediated by excitatory glutamatergic interneurons and N-methyl-D-aspartate (NMDA) receptors (Paulus et al., 2008; Reis et al., 2008; Schwenkreis et al., 2000; Ziemann, 2003, 2004). Results of SICI and ICF are expressed as percentage ratios of MEP amplitudes. These ratios represent the mean MEP amplitude of paired TMS over the mean MEP amplitude of the test stimuli baseline measurement (10 single magnetic pulses set at 120% rMT). Therefore, high SICI values reflect a lack of intracortical inhibition, whereas a low value ICF corresponds to a lack of intracortical facilitation. Finally, we measured long-interval cortical inhibition (LICI) through paired-pulse TMS of identical suprathreshold intensity (i.e. 120% rMT) with an ISI of 100ms. The first pulse corresponded to the conditioning stimulus whereas the second pulse was the test stimulus. LICI is primarily known to be mediated by $GABA_B$ receptors (McDonnell, Orekhov, & Ziemann, 2006; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). To calculate LICI, we

used the percentage ratio between the mean peak-to-peak MEP amplitude of the test stimulus response (TSR) and the mean peak-to-peak MEP amplitude of the conditioning stimulus response (CSR) expressed as: mean (TSR)/mean(CSR).

Statistics

Statistical analyses were performed using IBM SPSS Statistics software version 25 (Armonk, NY, United States). The Shapiro-Wilks test was used to determine the normality of the data. Parametric and nonparametric tests were performed, where appropriate, with a α-level fixed at 0.05. Descriptive analyses were used to characterize and compare the three groups (1- IULF patients with NRS$\geq$4; 2- IULF patients with NRS<4; 3- healthy controls) in our study sample. Results from descriptive analyses are expressed as means, standard deviation (SD), and percentages. We used a Student's t-test or a Mann-Whitney U test to investigate group differences on TMS measures. An analysis of variance (ANOVA) or the Kruskal-Wallis test were also used where appropriate. Pearson and Spearman's correlation analysis were also computed to assess the relationship between functional disability outcomes and the other outcome measures of interest (pain intensity and TMS measures). We corrected for multiple comparisons using False Discovery Rate (FDR) where appropriate. Post-hoc analyses were conducted to control for the effect of within-group variability of stimulated hemispheres across IULF patients on TMS measures as it varied according to the injury location (left or right). Therefore, we elected to create subgroups as follow: IULF patients stimulated over the left hemisphere (IULF with left-M1) and IULF patients stimulated on the right hemisphere (IULF with right-M1). Lastly, a post-hoc linear regression analysis was computed to assess which independent variables between pain intensity (NRS score from 0-10) and the number of days between the accident and testing (independent variable) best predict significant changes in M1-cortical excitability (dependent variable) in IULF patients.

Results

Demographic information

A total of 84 subjects took part in the current study, of which 56 had suffered an IULF (23 females; mean age: 39.41 years old) and 28 were healthy controls (17 females; mean age: 34.93). Two subgroups of IULF patients were formed according to pain intensity: Twenty-five IULF individuals met the criteria for moderate to severe pain (NRS ≥4), whereas 31 IULF subjects were classified as having mild pain (NRS <4). Age (H=3.89; p=0.14) and sex ($F_{(81)}$=3.76; p=0.15) did not differ between groups, whereas the level of education ($F_{(81)}$=3.95; p=0.02) and the time elapsed between the accident and testing (*U*=225.50; p=0.01) were statistically different across groups. More specifically, IULF patients with NRS≥4 were tested on average 4.48 (SD=3.50) days post-accident compared to 7.55 (SD=4.45) days for IULF patients with NRS<4. Spearman's correlational analyses revealed a strong association between pain intensity and the extent of functional disability as measured through the DASH questionnaire (r_s=0.76; p<0.001). Refer to tables 1-2 for additional descriptive information regarding study sample and fracture distribution among IULF patients.

Tableau 1. – Descriptive characteristics of study cohort by group

	IULF subgroup NRS ≥4	**IULF subgroup NRS <4**	**Healthy controls**	**Results of analysis**	**p-value**
N *(subjects)*	25	31	28		–
Age *(years [SD])*	42.36 (13.83)	37.03 (12.02)	34.93 (11.95)	*H*= 3.89	0.14
Sex *(female [%])*	12 (48%)	11 (35%)	17 (61%)	F= 3.76	0.15
Education *(years [SD])*	13.44 (2.65)	14.74 (2.86)	15.54 (2.65)	F= 3.95	0.02*
Number of days between trauma and	4.48 (3.50)	7.55 (4.45)	–	*U*= 225.50	0.01*

data collection/assessment *(days [SD])*					
Side of the stimulated hemisphere *(left [%])*	10 (40%)	17 (55%)	–	X^2= 1.22	0.30
NRS Actual pain *(SD)*	5.64 (1.41)	1.26 (1.00)	0.14 (0.36)	*H*= 65.46	<0.001*
DASH score *(SD)*	56.15 (16.56)	45.58 (17.43)	1.90 (3.04)	*H*= 56.55	<0.001*

Level of significance was set at p<0.05*

Tableau 2. – Fracture distribution among IULF patients

Type of fracture	**N (subjects [%])**
- Radial head	11(19.64)
- Collarbone	8 (14.29)
- Humerus	9 (16.07)
- Distal radius	21 (37.50)
- Scaphoid	4 (7.14)
- Scapula	1 (1.79)
- Ulna	2 (3.57)

Group differences on M1-cortical excitability measures in relation to pain threshold

Resting Motor Threshold (rMT)

Mann-Whitney U test revealed that IULF patients with NRS≥4 did not statistically differ from IULF patients with NRS<4 (*U*=324.50; p=0.54) and healthy controls (*U*=323.50; p=0.82) on rMT. Similarly, IULF patients with NRS<4 showed equivalent rMT measures as healthy controls (*U*=365.00; p=0.39). See Fig 1A.

MEPs test stimulus intensity

MEPs of the test stimulus used to measure SICI and ICF were equivalent between groups. Indeed, IULF patients with NRS≥4 did not statistically differ from IULF patients with NRS<4 (U=336.00; p=0.40) and healthy controls (U=304.00; p=0.41). Moreover, IULF patients with NRS<4 and healthy controls were comparable (U=431.00; p=0.96). See Fig 1B.

Short intra-cortical inhibition (SICI)

Results showed that IULF patients with NRS ≥4 statistically differed from healthy controls (*U*=202.00; p<0.01), with NRS ≥4 IULF patients exhibiting reduced short-intracortical inhibition of M1. A tendency toward reduced short-intracortical inhibition was found in IULF patients with NRS ≥4 compared to IULF patients with NRS <4, but the difference failed to reach significance (*U*=282.50; p=0.08). Lastly, IULF patients with NRS<4 and healthy controls showed similar SICI (*U*=383.00; p=0.44). See Fig 1C. We then conducted a post-hoc linear regression to assess the contribution of both pain intensity and delay between the accident and testing on SICI disinhibition. Data shows that pain intensity at the time of testing significantly predicted SICI disinhibition and explained 29% of the variance (β-coefficient = 0.29; p=0.05), whereas the delay between the accident and testing poorly predicted SICI disinhibition (β-coefficient= 0.07; 0.63).

Intra-cortical facilitation (ICF)

IULF patients with NRS≥4 exhibited a significantly reduced ICF ($t_{(54)}$=2.44; p=0.02) relative to IULF patients with NRS<4. IULF patients with NRS≥4 ($t_{(51)}$=-1.63; p=0.11) and IULF with NRS<4 ($t_{(57)}$=0.37; p=0.71) did not statistically differ from healthy controls. See Fig 1D. Results from a post-hoc linear regression showed that pain intensity significantly predicted altered ICF (β-coefficient=-0.30; p=0.04), accounting for 30% of the variance, whereas delay between the accident and testing (β-coefficient=-0.02; p=0.87) poorly predicted altered ICF.

Long-interval cortical inhibition (LICI)

IULF patients with NRS≥4 had similar LICI values compared to IULF patients with NRS<4 (*U*=339.00; p=0.42) and healthy controls (*U*=324.00; p=0.64). IULF patients with NRS<4 and healthy controls were also equivalent on LICI (*U*=405.00; p=0.66). See Fig 1E.

Figure 1. – Between group differences on TMS measures

Figure 1A. Between group comparison on rMT

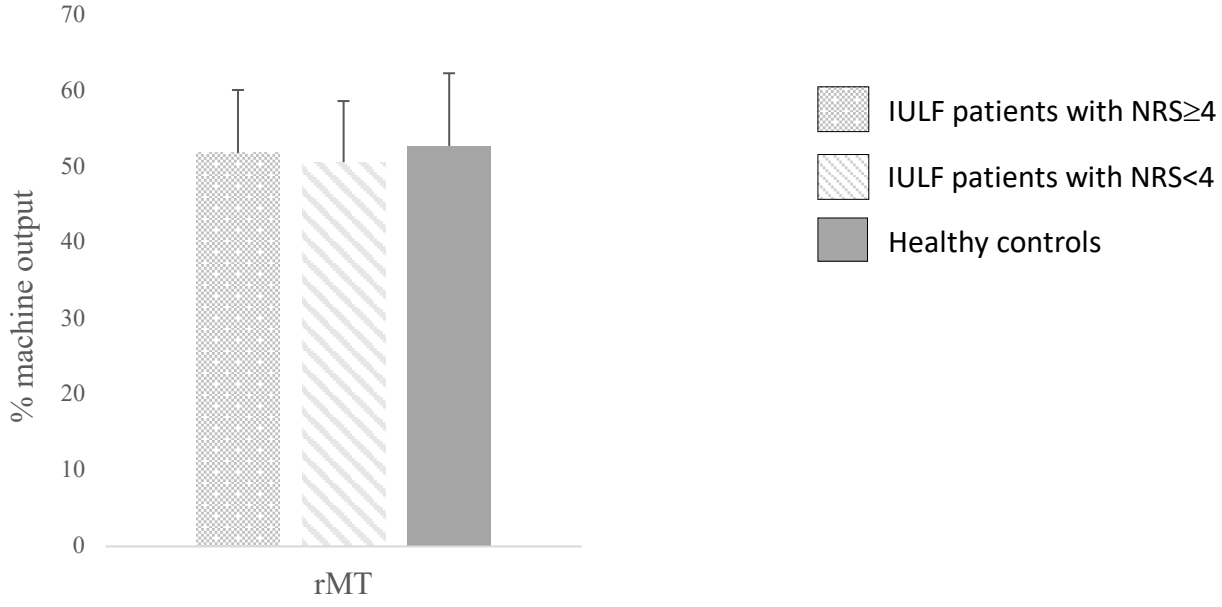


Figure 1B. Between group comparison on MEPs test stimulus intensity

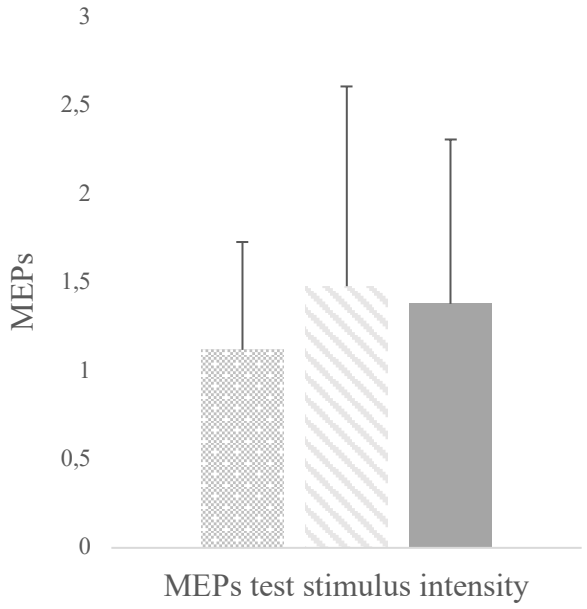


Figure 1C. Between group comparison on SICI

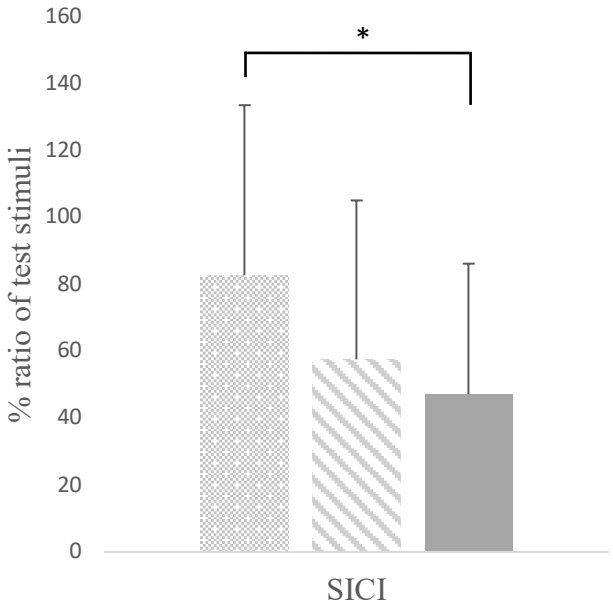


Figure 1D. Between group comparison on ICF

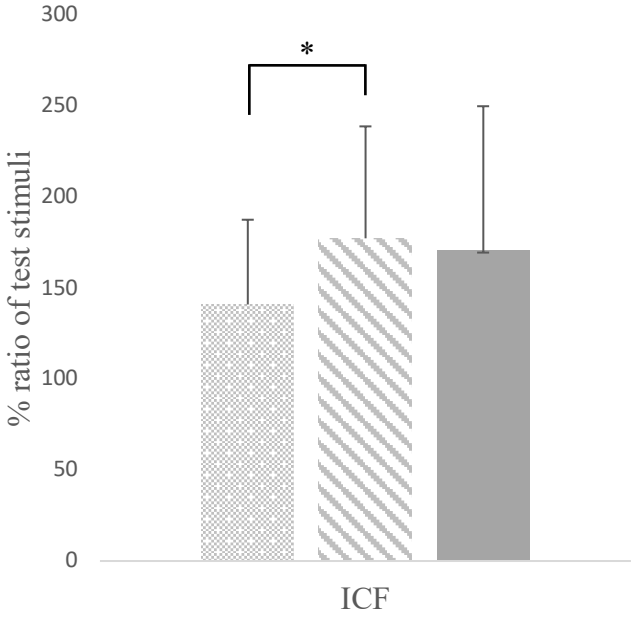
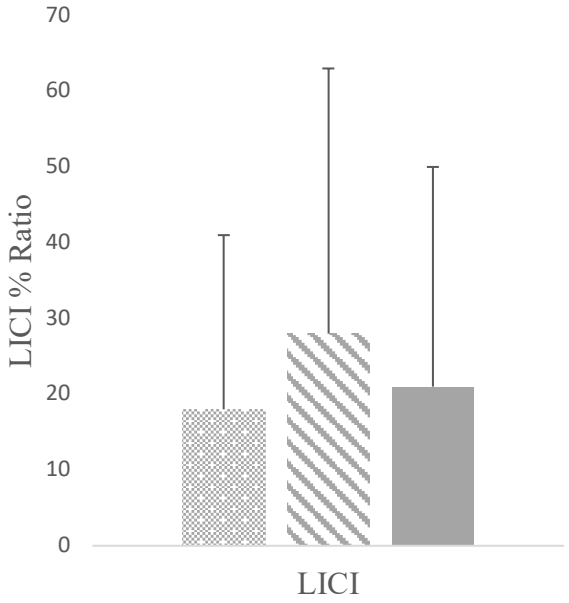


Figure 1E. Between group comparison on LICI



Post-hoc analyses controlling for the side of the stimulated hemisphere in IULF patients

To investigate if the stimulated hemisphere had an impact on cortical excitability measures, IULF patients were stratified into two distinct groups: IULF patients stimulated on the left M1 and IULF patients stimulated on the right M1. Demographic data such as age (*U*=296.00; p=0.12), sex ($X^2_{(1)}$=0.002; p=0.96), education level ($t_{(54)}$=1.17; p=0.25), and the timing of testing in relation to the accident (*U*=339.50; p=0.39) were similar across groups (see table 3). Lastly, there was no between-group difference in regard to pain intensity (U=297.50; p=0.12).

Tableau 3. – Descriptive characteristics of IULF patients according to the stimulated hemisphere

	IULF subgroup Left M1	**IULF subgroup Right M1**	**Results of the test analysis**	**p-value**
N *(subjects)*	27	29		–
Age *(years [SD])*	36.44 (12.40)	42.17 (13.18)	*U*= 296.00	0.12
Sex *(female [%])*	11 (41%)	12 (43%)	X^2= 0.002	0.96
Education *(years [SD])*	14.59 (3.06)	13.70 (2.51)	*t*= 1.17	0.25
Number of days between trauma and data collection/assessment *(days [SD])*	5.67 (3.92)	6.66 (4.65)	*U*= 339.50	0.39
NRS Actual pain *(SD)*	2.81 (2.83)	3.59 (2.13)	*U*= 297.50	0.12

Level of significance was set at p<0.05*

Group differences on M1-cortical excitability measures in relation to M1 stimulation side

None of the TMS measures differed across IULF patients according to the stimulated hemisphere [rMT (*U*=359.00; p=0.93); SICI (*U*= 377.00; p=0.81); ICF ($t_{(54)}$=-0.44; p=0.6); LICI (*U*= 361.50; p=0.62)]. See Fig 2A-D.

Figure 2. – Between IULF-group differences on TMS measures according the the stimulated hemisphere

Figure 2A. Between IULF-group differences on rMT stratified according to the stimulated hemisphere

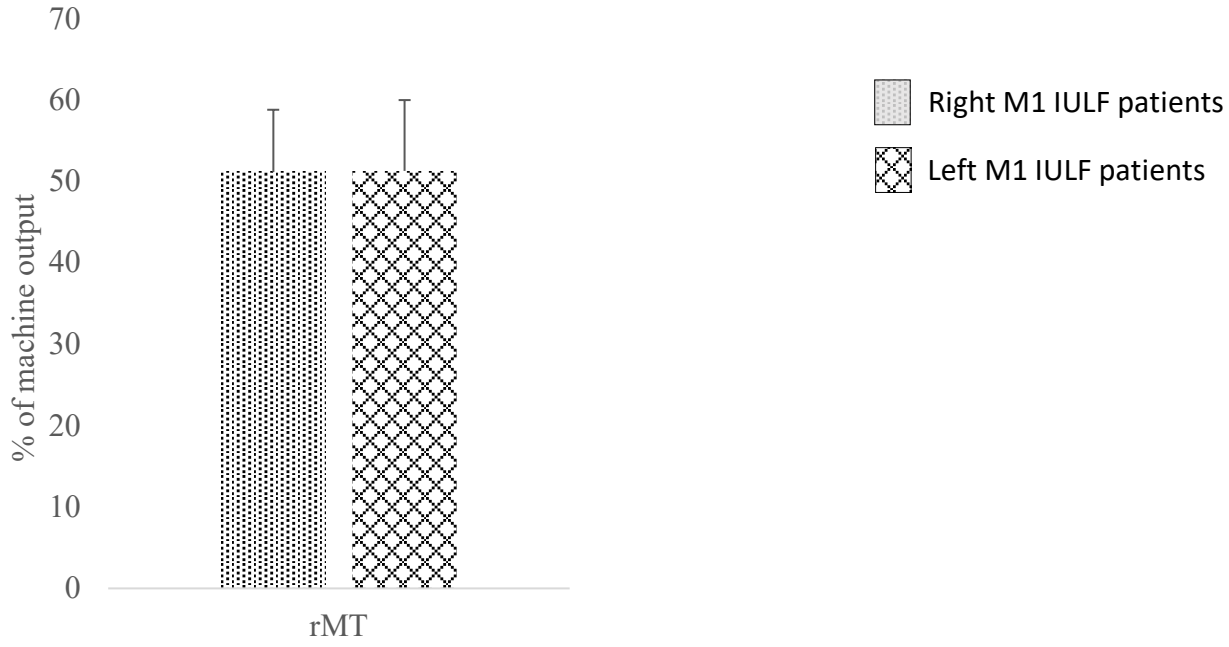


Figure 2B. Between IULF-group differences on SICI stratified according to the stimulated hemisphere

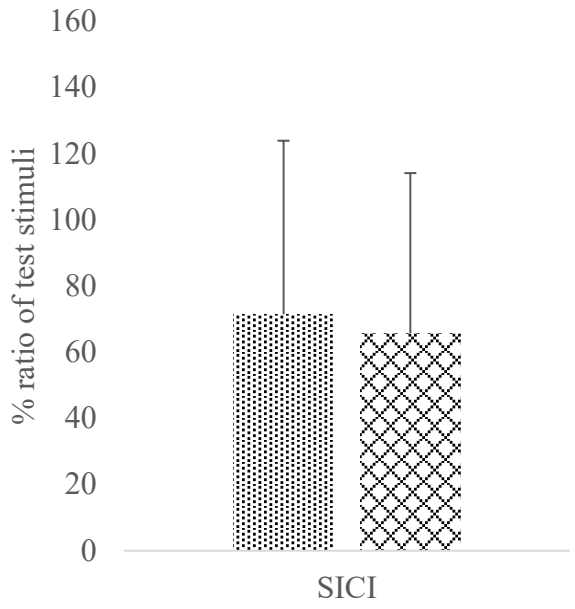


Figure 2C. Between IULF-group differences on ICF stratified according to the stimulated hemisphere

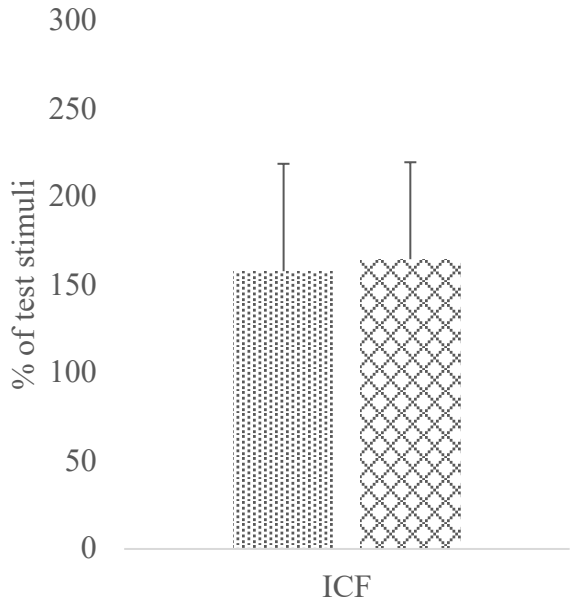
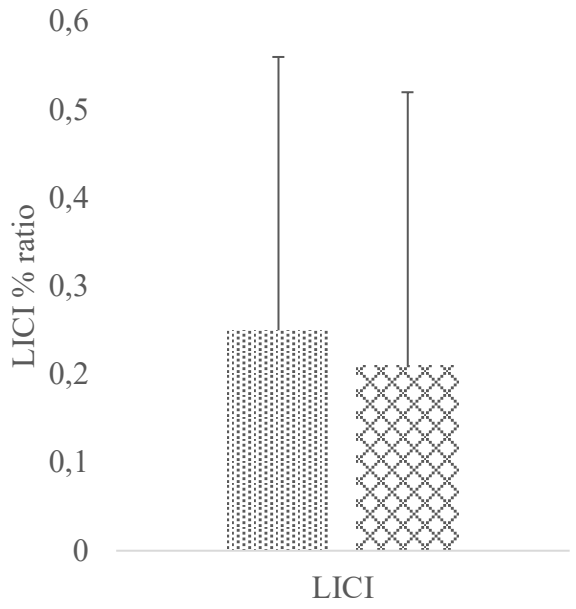


Figure 2D. Between IULF-group differences on LICI stratified according to the stimulated hemisphere



Relationship between cortical excitability measures and functional disability outcomes

The DASH questionnaire was used to investigate the relationship between functional disability outcomes and cortical excitability parameters. Only IULF subjects were included in this analysis, whereas healthy controls were excluded. Results show that the DASH score was strongly associated with SICI (R_s=0.37; p=0.006), whereas no correlation was found with ICF (r= -0.11; p=0.46), LICI (R_s=-0.06; p=0.67), and rMT (R_s= 0.18; p=0.22).

Discussion

This study provides new insights into the involvement of the primary motor cortex in the early phase of recovery (<14 days post-trauma) following an IULF through various TMS protocols assessing M1-cortical excitability. More precisely, results suggest a significant decrease in intracortical inhibition and facilitation in IULF patients over the cortical representation of the fractured bone. These neurophysiological alterations were only observed in IULF patients with

pain of moderate to severe intensity (NRS ≥4), whereas IULF patients with mild pain did not differ from healthy controls. Furthermore, this study highlights that the time elapsed between the accident and testing within the first 14 days of the accident, as well as the stimulated hemisphere, do not influence any of the primary motor cortex excitability measures. On the contrary, pain intensity emerges as the main factor explaining acute abnormalities of M1 excitability in IULF patients relative to a healthy cohort of similar age, sex distribution, and education level. To the best of our knowledge, this is the first study to investigate M1-cortical excitability in acute pain following an isolated upper limb fracture.

This study suggests a state of disinhibition through reduced SICI, a TMS measure that is robustly associated to $GABA_A$ receptors activity (Ziemann, 2003), but only in patients with moderate to severe pain intensity (NRS ≥4). Moreover, the extent of SICI disruption was strongly associated with functional disability scores (DASH). Current findings highlight possible resemblance across pain states, as SICI disturbances are also found in various chronic pain conditions (Eisenberg et al., 2005; Mhalla, de Andrade, Baudic, Perrot, & Bouhassira, 2010; Parker et al., 2016; Schwenkreis et al., 2003). A reduction of GABAergic inhibition has been shown to play a prominent role in chronic pain development and in pain maintenance (Knabl et al., 2008). It is therefore no surprise that GABA receptor agonists have proven effective as an analgesic agent, but important side effects limit its long-term use (Enna, Harstad, & McCarson, 1998; Jasmin, Wu, & Ohara, 2004). Identification of a state of disinhibition at such an early stage of recovery in patients with a fracture is of particular clinical relevance in this population since high initial pain is considered a risk factor for chronic pain development (Lavigne, Khoury, Chauny, & Desautels, 2015). These results may further our understanding as to why high levels of pain in the acute phase is considered a risk factor for chronic pain. Indeed, patients with moderate to severe pain (NRS ≥4) are affected by disrupted GABAergic inhibition within the first few days post-trauma, which may hypothetically contribute to CNS' vulnerability to pain chronification.

Of note, current findings diverge from results found in experimental acute pain studies. Experimentally induced pain in healthy controls shows an increase in M1 intracortical inhibition whereas the current study found a decrease in inhibition in IULF patients presenting with moderate to severe acute pain (NRS ≥4). Increased SICI in acute experimental pain has been

suggested as an adaptation strategy to prevent CNS reorganization (Salo, Vaalto, Koponen, Nieminen, & Ilmoniemi, 2019). Given the reverse pattern of M1 disinhibition in IULF patients, one should investigate whether moderate to severe pain symptoms in the latter clinical population may facilitate lasting CNS reorganization through sustained activation of plasticity mechanisms. One reason for the discrepancies in SICI findings between experimental and acute clinical pain could be that fracture pain involves multiple physiological mechanisms that cannot be replicated in a human experimental setting. For example, the physiological cascade following tissue injury and bone fracture alone, including an acute inflammatory response, can modulate brain excitability (Galic, Riazi, & Pittman, 2012) and impair GABAergic and glutamatergic activities (Cooper & Przebinda, 2011). Future studies combining both experimental paradigms in a healthy cohort and clinical pain in OT patients are warranted if we are to investigate the mechanisms involved and to restrict results discrepancy due to possible methodological variabilities.

Current results also reveal alterations of intracortical facilitation in IULF patients with moderate to severe pain (NRS $\geq$4), a measure traditionally considered to be mediated by glutamatergic facilitatory transmission (Paulus et al., 2008; Reis et al., 2008; Schwenkreis et al., 2000; Ziemann, 2003, 2004). The finding that both ICF and SICI are reduced may appear counterintuitive from a physiological standpoint. However, physiological underpinnings of TMS-induced ICF effects have been the subject of ongoing debate, as some evidence suggest that the latter reflects an overlap between inhibitory and excitatory mechanisms (Reis et al., 2008). Along those lines, pharmacological studies have shown that both NMDA receptors antagonists (such as dextromethorphan and memantine) as well as $GABA_A$ agonists can modulate ICF. In parallel, some TMS and chronic pain studies have shown reduced ICF, but this was mainly found in patients with fibromyalgia (Lefaucheur et al., 2006; Mhalla et al., 2010). Additional factors relevant to the orthopedic population could also account for current study findings. For example, other types of pain (muscle pain, bone pain, etc.) and inflammatory response can influence the balance between inhibitory and facilitatory mechanisms (Cooper & Przebinda, 2011; Galic et al., 2012). Moreover, limb disuse may also affect brain plasticity due to reduced sensorimotor input and output (Clark, Taylor, Hoffman, Dearth, & Thomas, 2010; Langer, Hanggi, Muller, Simmen, & Jancke, 2012; Liepert, Tegenthoff, & Malin, 1995).

Current findings support work from Pelletier and colleagues (Pelletier et al., 2017) suggesting that pain intensity, rather than pain state, appears to be linked to the extent of motor cortex excitability alterations. As such, patients who reported moderate to severe pain (NRS $\geq$4) showed accentuated SICI and ICF alterations as compared to patients with mild pain levels who showed a similar M1 excitability profile to healthy controls. This is particularly interesting as results from the current study showed that patients with higher pain levels also reported greater functional disability. Therefore, study findings are not only consistent with the notion that high initial pain is a good predictor for chronic pain, but it also argues that altered cortical excitability of M1 could contribute to underlying mechanisms of pain chronification following a fracture (Mehta, MacDermid, Richardson, MacIntyre, & Grewal, 2015; Moseley et al., 2014).

Although a similar M1-cortical excitability profile may emerge between acute and chronic injury phases, the involvement of the CNS may be different. One should bear in mind that altered SICI and ICF in acute pain do not necessarily indicate permanent CNS reorganization. Although speculative, acute changes in M1-cortical excitability could also reflect the intensity of the nociceptive afferent originating from the periphery. It should be noted that the group of patients reporting moderate to severe (NRS $\geq$4) pain levels who also exhibited altered M1-cortical excitability were tested at a significantly shorter delay following the accident relative to patients who reported mild levels of pain. One cannot exclude the possibility that alterations of M1-cortical excitability within the first few days of the injury could have subsided as pain intensity is expected to reduce with additional time to recover. However, results from linear regressions, used to delimitate the weight of the timing of testing in relation to the accident and pain intensity on altered M1-cortical excitability, showed that pain intensity best predicted altered intracortical inhibition and facilitation, whereas timing of testing had no impact within that short 14-day time frame. Longitudinal follow-ups are nonetheless needed to investigate longitudinal changes of TMS-induced M1 excitability measurements in relation with pain stages, particularly during the transition from acute to chronic pain.

LICI, another measure reflecting $GABA_B$ receptors inhibition, was found to be unrelated to reported pain intensity following a peripheral injury. In a recent review, authors only found scarce evidence of the involvement of LICI alterations in various chronic pain conditions (Parker et al.,

2016), either suggesting that $GABA_B$ receptors remain intact or that the latter measure may be less sensitive to pain states. It would still appear relevant to include other TMS paradigms known to measure $GABA_A$ and $GABA_B$ receptors, namely short-afferent inhibition (SAI), long-afferent inhibition (LAI), and the cortical silent period (CSP) in the context of future studies (Reis et al., 2008; Turco et al., 2018). This would allow us to deepen our understanding of the involvement of acute pain on the GABAergic inhibitory system in IULF patients.

Given the known durable effects of multisession rTMS protocols on M1-cortical excitability and on pain reduction, rTMS appears as a highly relevant intervention avenue for the IULF population. Acute rTMS application should be considered as an intervention option as it may provide analgesic effects to suffering patients, in addition to possibly tackling cortical excitability changes associated with pain chronification.

One limitation to the current study is the use of a single TMS session to investigate M1-cortical excitability implications in the acute phase of an IULF in relation to pain intensity. Longitudinal studies are needed among this population to further explore the effects of early M1-cortical excitability dysregulations on recovery. This would provide valuable insights as to whether acute altered M1-cortical excitability is a predictor of pain chronification. Secondly, this study uses limited, but well established, TMS parameters. Still, it should be considered that TMS parameters vary greatly across studies (e.g. ISI, test and conditioned stimuli intensity), surely contributing to result variability found in the literature. This poses a challenge for researchers to establish the most sensitive and specific TMS parameters. In the context of the present study, it should be considered that previous studies have highlighted possible contamination by short-afferent cortical facilitation (SICF) in SICI according to the TMS parameters used (Garry & Thomson, 2009; Peurala, Muller-Dahlhaus, Arai, & Ziemann, 2008). Although the present study uses parameters from previously published studies, SICF contamination cannot be excluded. It would be important to account for these findings in future studies. Moreover, the use of additional TMS paradigms (SAI, LAI, CSP) as well as an objective measure of pain, such as conditioned pain modulation (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016; Yarnitsky, 2010), would be highly relevant in the context of future studies to draw a thorough physiological profile of ascending and descending tracks in IULF patients with moderate to severe pain (NRS $\geq$4). Thirdly, since the initial medical

consultations varied across IULF individuals, timing of testing post-accident was not equivalent within the IULF group. Although post-hoc analyses showed that this factor did not influence TMS outcomes, future studies should, to the extent possible, assess patients at a fixed day since the physiological cascade following the injury is rapidly evolving. Fourthly, pain medication usage and dosage at the time of testing were not restrained in IULF patients, possibly leading to interindividual variability among the sample. Effects of analgesics medication on cortical excitability measures cannot be excluded although very scarce evidence exists. One study showed that acetaminophen can increase MEP, which facilitates the inhibition of voltage-gated calcium and sodium currents (Mauger & Hopker, 2013). In this case, and in relation with current study results showing decreased intracortical inhibition, acetaminophen usage among study sample could have masked cortical excitability deficiencies. As for opioid analgesics, only one study mentioned that fentanyl does not alter MEP amplitudes (Ziemann, 2004), a drug that is rarely used to treat acute pain. Fifthly, future studies should also account for additional factors, such as the inflammatory cascade (pro-inflammatory cytokines levels) and genetic predisposition, as they are known to impact pain intensity and M1-cortical excitability measures (Calabrese et al., 2014; Caumo et al., 2016; Mori et al., 2011; Vezzani & Viviani, 2015). Accounting for such factors would be beneficial to develop tailored interventions for the IULF population. Sixthly, the stimulated hemisphere (right or left M1) varied in IULF patients according to the injured side. This factor was controlled for in IULF patients and no differences were found. On the other hand, all healthy controls were right-handed and were stimulated on the left-M1, which corresponds to the dominant hemisphere as per optimal TMS guidelines. Since no differences were found among the clinical sample, we elected to follow the TMS guidelines in the healthy sample. Finally, evidence show that reduced use of limb (limb immobilization) can indeed lead to brain changes (cortical thickness, cortical excitability, etc.) in the motor cortex due to reduced sensory input/sensorimotor deprivation (Clark et al., 2010; Langer et al., 2012; Liepert et al., 1995; Zanette, Manganotti, Fiaschi, & Tamburin, 2004). We can by no mean exclude this factor entirely, but a few points should be considered. First, IULF patients were tested very early post-injury, leaving less time for measurable brain changes. Second, statistical analyses show that the number of days between testing and the accident (possible indicator of reduced limb use) is not associated

with alterations in cortical excitability measures. Lastly, IULF patients who showed most cortical excitability deficiencies were actually tested within shorter delays of accident (NRS >4 group), leaving less time, compared to the other IULF group (NRS<4), for cortical reorganization due to limb immobilization.

Conclusions

In conclusion, this is the first study to investigate M1 cortical excitability involvement in an orthopedic trauma population suffering from acute pain. Current results show early signs of altered GABAergic inhibitory and glutamatergic facilitatory activities in patients with pain of moderate to severe intensity (NRS $\geq$4). These findings may bear major clinical significance as this population is vulnerable to chronic pain development. Early detection of at-risk patients could guide proactive intervention aiming to reduce the likelihood of an unsuccessful recovery in this population, leading to a pathological condition. This study also highlights that acute application of rTMS may reveal promising in alleviating pain symptoms among this population and may have implications in preventing chronic pain development.

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Chapitre 3 – Discussion générale

Rappel des objectifs et synthèse des résultats

Cette thèse visait à investiguer l'incidence de TCCL concomitant à une fracture isolée ainsi que son impact sur la récupération orthopédique. Cette thèse s'est également penchée sur les mécanismes physiologiques impliqués en contexte de fractures étant accompagnées, ou non, de blessures traumatiques, en adoptant une approche clinique et théorique. Cette démarche avait notamment pour but de faire avancer la réflexion sur le développement de techniques thérapeutiques pouvant améliorer la récupération fonctionnelle au sein des populations aux prises avec une blessure traumatique. Ainsi, cette thèse est composée de six articles, dont cinq expérimentaux. Un résumé de leurs objectifs respectifs ainsi qu'une synthèse des résultats seront d'abord présentés, puis discutés.

Étude 1

La première étude visait d'abord à déterminer l'incidence de TCCL, obtenue à partir d'un dépistage exhaustif réalisé rétrospectivement, chez des personnes qui ont subi une fracture isolée. Ensuite, l'étude visait à établir la proportion de cas de TCCL non dépistés au DU selon l'incidence de TCCL obtenue rétrospectivement. Enfin, cette étude visait à déterminer le risque de subir un TCCL concomitant selon l'emplacement de la fracture du patient. Les résultats ont révélé que 23,5% des patients avec une fracture isolée présentaient un TCCL concomitant, bien que 62,7% des TCCL n'avaient pas été diagnostiqués au DU. Cette étude a également démontré que la proximité anatomique de la fracture par rapport à la tête constituait un facteur étroitement associé au risque de subir un TCCL concomitant. Plus spécifiquement, les patients qui ont subi une fracture du membre supérieur sont significativement plus à risque de subir un TCCL concomitant (29,6%) en comparaison aux patients aux prises avec une fracture du membre inférieur (15,6%). Lorsqu'on explore davantage le lien soupçonné entre la proximité anatomique de la fracture par rapport à la tête en formant deux groupes distincts parmi les fractures au membre supérieur, soit les fractures distales (radius, cubitus, poignet, main) et les fractures proximales (omoplate, clavicule, humérus), ces dernières sont plus fréquemment associées à un TCCL (40,6% versus 20,3%). Ceci renforce à nouveau le lien entre la proximité anatomique de la fracture par rapport à la tête et le risque de subir un TCCL.

Étude 2

La deuxième étude visait, quant à elle, à évaluer les effets de subir un TCCL concomitant à une fracture isolée sur le degré d'intensité de douleur ressentie en phase post-aiguë (< trois mois post-accident). Les résultats ont révélé que les participants du groupe fracture+TCCL estimaient plus sévèrement la douleur ressentie depuis leur accident ainsi qu'au moment de la collecte de données comparativement à leurs homologues avec fracture, mais sans TCCL. Cette distinction était présente même après avoir contrôlé plusieurs facteurs pouvant moduler la perception de douleur. Ainsi, la présence d'un TCCL semble exacerber la douleur ressentie chez des patients souffrant d'une fracture isolée.

Étude 3

La troisième étude visait à documenter le nombre de jours avant de retourner au travail par des patients travailleurs aux prises avec une fracture isolée selon la présence, ou non, d'un TCCL concomitant. Les résultats ont montré que les patients avec fracture+TCCL prennent deux fois plus de temps pour retourner au travail que les patients avec fracture, mais sans TCCL (329,7 jours versus 150,3 jours). L'écart entre les deux profils de patients devient davantage marqué après avoir contrôlé pour l'impact démontré du recours aux agents payeurs sur le délai nécessaire pour réintégrer le travail (299,4 jours versus 105,2 jours). En outre, cette étude a montré que près d'un patient sur cinq (19,5%) du groupe fracture+TCCL n'était pas retourné au travail au moment de la collecte de données, soit environ 21 mois post-accident, malgré leur intention de le faire, contrairement à 6,34% pour le groupe « fracture seule ». Ces résultats suggèrent que de subir un TCCL en contexte de fractures isolées nuit à un retour au travail rapide, et ce, chez des patients qui sont majoritairement dans la force de l'âge en termes de productivité au travail.

Étude 4

La quatrième étude avait pour objectif d'explorer l'association entre la présence d'un TCCL concomitant à une fracture et l'incidence d'ossification hétérotopique. Les résultats de cette étude ont démontré que le développement d'ossification hétérotopique est significativement plus fréquent chez les patients atteints à la fois d'une fracture et d'un TCCL (46,0%) par rapport aux patients souffrant d'une fracture sans TCCL (26,3%) et ce, même après avoir contrôlé diverses

variables. Cette étude a également démontré qu'au sein du groupe fracture+TCCL, la présence d'ossification hétérotopique était étroitement associée à un plus long délai avant le retour au travail, comparativement aux sujets fracture+TCCL ne montrant aucun signe d'ossification hétérotopique. Cette association n'était toutefois pas présente au sein du groupe de patients avec une fracture seule, à savoir que les patients avec fracture seule chez qui des signes d'ossification hétérotopique avaient été détectés retournaient au travail suite à un délai similaire à celui des patients avec fracture seule, mais sans signe d'ossification hétérotopique. Ainsi, l'impact fonctionnel d'ossification hétérotopique semble être plus considérable chez les personnes avec une fracture lorsque combinée à un TCCL qu'en l'absence de TCCL.

Étude 5

La cinquième étude est une revue de la littérature qui visait à s'interroger plus spécifiquement sur l'utilité clinique de la SMT et de sa forme interventionniste, la SMT répétée (SMTr), pour investiguer et intervenir sur les mécanismes physiologiques contribuant au processus de transition de la douleur aiguë à la douleur chronique chez les patients souffrant de blessures de nature traumatique. Selon la revue de la littérature, la SMT a le potentiel d'être un bon outil d'investigation en contexte de blessures traumatiques grâce à sa capacité à suivre et à objectiver certains mécanismes associés à la sensibilisation centrale (débalancement entre les systèmes GABAergique et glutaminergique). Ensuite, les études du domaine pointent vers la pertinence de développer des protocoles cliniques afin d'investiguer l'application de la SMTr dans le traitement de la douleur aiguë chez des populations aux prises avec un large éventail de blessures traumatiques. En effet, les données probantes semblent suggérer que la SMTr détient la capacité d'intervenir sur certains mécanismes pathophysiologiques clés contribuant à la transition de la douleur aiguë vers la douleur chronique.

ÉvaluaÉtude 6

La sixième étude avait pour but d'évaluer l'association entre l'intensité de douleur perçue en phase aiguë chez des patients victimes d'une fracture isolée du membre supérieur et les mécanismes d'excitabilité corticale du cortex moteur primaire. Les résultats ont démontré une atteinte spécifique des mécanismes d'inhibition et de facilitation intracorticale du cortex moteur

primaire chez les patients avec fracture qui rapportaient un niveau de douleur modéré à sévère. Au contraire, les patients présentant une douleur d'intensité légère ne différaient pas des sujets témoins sains sur le plan des mesures d'excitabilité corticale. Le degré d'atteinte des mécanismes d'inhibition et de facilitation intracorticale était associé au degré d'atteinte fonctionnelle. Ainsi, cette étude a démontré, d'une part, une atteinte des mécanismes d'excitabilité corticale en phase aiguë post-fracture. D'autre part, les résultats suggèrent que l'intensité de la douleur semble se démarquer comme étant un facteur à l'origine des anomalies neurophysiologiques du cortex moteur primaire chez les patients en phase aiguë post-fracture.

Liens entre la littérature et les résultats des études

La section suivante abordera l'impact des résultats de la présente thèse sur la pratique clinique actuelle et sur le domaine scientifique concernant la population d'intérêt.

Défis liés au diagnostic du TCCL au département d'urgence lorsque le patient se présente avec une fracture

L'incidence trop élevée de TCCL non dépistés est une problématique connue (Buck, 2011). La première étude de cette thèse appuie cet enjeu, mais met également en lumière la présence d'autres éléments à considérer. En effet, la littérature suggère que le taux élevé de TCCL non dépistés est surtout attribuable au fait que les gens ne sont pas portés à consulter pour une telle condition par manque de connaissances sur le TCCL, la présence de symptômes plutôt bénins et difficilement identifiables, et/ou l'apparition tardive des symptômes (Setnik & Bazarian, 2007). Or, la situation dépeinte dans l'article 1 est différente, car il s'agit de personnes consultant au DU et qui, en dépit d'un accès à une équipe médicale, reçoivent leur congé médical sans diagnostic de TCCL. L'hypothèse à privilégier dans ce contexte semble être que l'attention du patient et de l'équipe médicale soit davantage accordée à la blessure visible et particulièrement souffrante, soit la fracture. À cela s'ajoutent d'autres hypothèses, plus spécifiques à la situation au Québec, tels qu'on peut le lire dans un document publié en 2018 par l'Institut National d'Excellence en Santé et en Services Sociaux (INESSS) (INESSS, 2018). En dépit de critères diagnostics clairs pour le dépistage de TCCL au Québec, l'INESSS soulève que l'état de conscience est souvent évalué rapidement et sommairement au DU, possiblement car le contexte s'y prête moins. Le document

fait également état d'une difficulté à investiguer et dépister d'autres symptômes plus subtils, quoique plus discriminatifs (p.ex. : troubles de coordination et/ou d'équilibre et une altération transitoire du champ visuel) dans ce département, un environnement à fort débit. Ces limites au niveau du dépistage de TCCL au DU peuvent s'avérer particulièrement problématiques auprès de patients se présentant au DU pour une fracture. En effet, une évaluation approfondie et exhaustive est de mise chez cette population considérant que la douleur générée par la fracture peut, en soi, altérer l'état de conscience. Il est donc primordial d'investiguer l'origine de certains symptômes auto-rapportés qui sont, à première vue, non-spécifiques (p.ex. : confusion découle de la douleur versus du TCCL ?) afin d'effectuer un diagnostic juste. Dans ce contexte, le rôle du DU pourrait être de dépister les patients à haut risque de TCCL concomitant, selon, par exemple, la nature des symptômes auto-rapportés, les mécanismes d'accident et la proximité anatomique de la fracture par rapport à la tête. Ensuite, une requête à une équipe de traumatologie pourrait être formulée afin qu'un dépistage exhaustif soit effectué dans les plus brefs délais dans un endroit plus propice. Un dépistage précoce facilitera la prise en charge de ces patients et l'accès aux ressources nécessaires pour optimiser la récupération.

Les conséquences du non diagnostic du TCCL au DU sont potentiellement importantes. En effet, les résultats des études de la présente thèse démontrent l'impact que peut avoir le TCCL sur la récupération fonctionnelle de la population orthopédique (douleur, retour au travail retardé, risque d'ossification hétérotopique). Ces résultats appuient les observations d'autres études dans la littérature qui montrent une association significative entre un TCCL non diagnostiqué et le risque de complications (Ponsford et al., 2002; Wade, King, Wenden, Crawford, & Caldwell, 1998). L'absence de diagnostic empêche également les patients d'avoir accès aux recommandations cliniques (documentation) et à une possible prise en charge, deux facteurs favorables à un meilleur pronostic (Larson-Dupuis & De Beaumont, 2016; Levin & Diaz-Arrastia, 2015; Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012; Ponsford et al., 2002; Prince & Bruhns, 2017). Ces patients sont donc potentiellement à risque de se chroniciser et de développer des complications pour une condition clinique qui n'a pas été identifiée. Ainsi, ces résultats soulèvent, d'une part, l'importance de sensibiliser le personnel médical impliqué dans les soins de patients avec fracture au fait que les TCCL passent souvent inaperçus chez cette population. D'autre part, des pistes de

solution devraient être présentées afin d'outiller les équipes médicales concernées à combattre et minimiser l'impact de cette réalité.

Pourquoi la présence d'un TCCL peut nuire à la récupération d'une fracture?

La thèse démontre que la présence d'un TCCL concomitant à une fracture isolée peut augmenter : 1) la perception de douleur, 2) le délai nécessaire pour retourner au travail, 3) le risque de développer de l'ossification hétérotopique. Ces associations ont précédemment été démontrées en contexte de blessures plus sévères (multiples TO et TCC modéré/sévère) (Bajwa et al., 2018; Coelho & Beraldo, 2009; Dizdar et al., 2013; Peixoto, Hyland, Buchanan, Langille, & Nahas, 2018). Toutefois, il existait peu d'évidences de telles associations chez les blessés considérés plus « légers ». Néanmoins, il est possible de s'inspirer des études réalisées auprès de populations blessées plus sévèrement et s'intéressant aux mécanismes physiologiques afin de fournir des pistes de réflexion sur les origines physiopathologiques des résultats obtenus dans la présente thèse. C'est d'ailleurs dans cette perspective qu'a été réalisée la revue de littérature (étude 5) portant sur les mécanismes physiopathologiques en contexte de blessures traumatiques. En effet, les TCC et les fractures, bien que distincts à plusieurs niveaux, partagent des mécanismes physiologiques impliquant, en phase aiguë comme en phase chronique, l'interaction entre le SNC et le système immunitaire (Franco, Pacheco, Lluis, Ahern, & O'Connell, 2007; Grace, Hutchinson, Maier, & Watkins, 2014; Ji, Xu, & Gao, 2014). Ces mécanismes jouent un rôle dans le processus de récupération normale, mais aussi dans le processus de récupération pathologique. En effet, en contexte pathologique, on retient que le développement d'ossification hétérotopique et la chronicisation de la douleur surviennent notamment lorsqu'il y a un bris au niveau du processus physiologique normal de guérison (Nauth et al., 2012). Ainsi, en contexte de doubles blessures (TCC et fracture), l'interaction entre les mécanismes physiologiques de ces deux blessures semble promouvoir l'installation du processus pathologique (Baba et al., 2003; Lin, Peng, & Willis, 1996). Par exemple, des études ont montré que l'ajout d'une fracture tibiale chez une souris qui a subi un TCC augmente la neuroinflammation comparativement à un groupe de souris avec TCC seul (Shultz et al., 2015). Une association entre la neuroinflammation exacerbée en contexte de doubles blessures et la sévérité des symptômes cliniques en phases aiguë et chronique a également été démontrée par cette équipe de chercheurs. Le patron inverse a aussi été observé,

soit que l'ajout d'un TCC à une fracture nuit à la récupération de souris aux doubles traumatismes comparativement à un groupe présentant une fracture seule (Rowe et al., 2016). Une perturbation au niveau de la perméabilité de la BHE causée par le TCC semble faciliter le passage ascendant et descendant des médiateurs inflammatoires et la communication entre le système nerveux central et périphérique (Evans et al., 2012; Morganti-Kossmann et al., 2001). Fait intéressant, une altération de la BHE est reconnue comme étant un facilitateur pour le développement de douleur chronique et d'ossification hétérotopique (DosSantos, Holanda-Afonso, Lima, DaSilva, & Moura-Neto, 2014; Huang et al., 2018; Huber et al., 2001; Varatharaj & Galea, 2017). La plus grande perméabilité de la BHE est également un mécanisme qui a été suggéré pour expliquer que certains symptômes du TCC peuvent se manifester à distance de l'insulte initiale (la tête), telle une sensation de douleur aux niveaux des jambes ou des bras (King et al., 2015; Lucas, 2015). À cela s'ajoutent d'autres évidences dans la littérature montrant que le TCC peut, à lui seul, altérer la guérison de la fracture et réduire la masse osseuse (Bajwa et al., 2018), ce qui peut expliquer l'incidence augmentée d'ossification hétérotopique objectivée dans l'étude 3. Selon Bajwa et collègues (2018), le TCCL pourrait provoquer une défaillance au niveau des hormones de croissance et de facteurs de croissance analogues à l'insuline via une altération de l'axe hypothalamo-pituaire. Ce débalancement pourrait être rétabli en administrant un traitement à base d'hormones de croissance, mais les effets de ce type de thérapie demeurent mitigés à ce jour, surtout au sein d'études cliniques (Bajwa et al., 2018; Raschke et al., 2007; Schmidmaier et al., 2002).

Planifier le retour au travail à la suite d'une fracture : devons-nous considérer la présence d'un TCCL?

Il existe plusieurs enjeux associés à un arrêt de travail prolongé. En effet, un retour au travail retardé place les personnes à haut risque de développer d'autres problèmes d'ordres physique (risque de développer des complications orthopédiques, apparition de symptômes associés à l'inactivité, augmentation des symptômes cardiovasculaires, respiratoires et de douleur, etc.) et psychologique (détresse psychologique, symptômes dépressifs, isolement, etc.), sans compter les enjeux financiers (van der Noordt, Jzelenberg, Droomers, & Proper, 2014). Le délai typiquement requis pour retourner au travail post-fracture de grade léger (un os fracturé) et post-TCCL varie

grandement selon les études consultées, mais celui-ci dépasse rarement 3 mois pour les fractures et de 3 à 6 mois pour les TCCL (Cancelliere et al., 2014; Sluys, Shults, & Richmond, 2016; Waljas et al., 2014). Or, l'étude 3 expose une situation inquiétante en contexte de doubles blessures. En effet, en moyenne, 329,7 jours, soit plus de 10 mois, se sont avérés nécessaires pour retourner au travail chez les patients fracture+TCCL, une augmentation de la durée qui est presque triplée par rapport au délai attendu en contexte de blessure isolée (TCCL seul et fracture seule). Sachant que la douleur et l'ossification hétérotopique sont deux facteurs associés à un délai prolongé, il est possible que ceux-ci contribuent au délai de retour au travail. Ces résultats démontrent l'importance de considérer la présence d'un TCCL concomitant dans la planification du retour au travail post-accident chez des patients récupérant d'une fracture. Des ressources devront être mises en place afin de maximiser la récupération et minimiser les impacts précédemment soulevés étant associés à un arrêt de travail prolongé. Dans ce contexte, le patient devrait être encouragé à retourner au travail dès que le médecin traitant jugera convenable et ce, même si un ajustement au niveau des tâches pré-accidentelles doit être fait. L'équipe médicale pourrait s'assurer de moduler les attentes du patient et de l'employeur durant le processus de réintégration au travail.

Mécanismes physiologiques de la douleur en contexte de fracture

L'étude 6 apporte un nouvel éclairage sur l'impact présumé de la douleur aiguë sur les mécanismes d'excitabilité corticale du cortex moteur primaire. À ce jour, seules des données issues d'études expérimentales effectuées auprès de sujets sains permettaient de comprendre l'impact de la douleur aiguë sur les mécanismes d'excitabilité corticale. Or, aucune étude clinique n'avait été réalisée et l'extrapolation de données expérimentales à des populations cliniques comprend son lot de limites. Les résultats de l'étude 6 révèlent une réduction des mécanismes inhibiteurs et facilitateurs intracorticaux du cortex moteur primaire chez les sujets vivant avec une fracture isolée du membre supérieur qui rapportent un niveau de douleur modéré à sévère. Au contraire, les patients rapportant de la douleur d'intensité légère présentaient un profil d'excitabilité corticale similaire à celui des sujets témoins sains. Ces trouvailles mettent en lumière des similarités au niveau du profil d'atteintes des sujets souffrant de douleur modérée/sévère en phase aiguë, lorsque comparés aux populations souffrant de douleur

chronique. L'identification de cette perturbation à un stade aussi précoce de la guérison, soit dans les premiers 14 jours post-fracture, est d'une importance clinique qui mérite d'être investiguée davantage. Ceci est particulièrement important dans un contexte où un niveau élevé de douleur en phase aiguë serait prédicteur du risque de chronicisation de l'état clinique (Lavigne et al., 2015), notamment en exacerbant la vulnérabilité du SNC. Cette hypothèse n'a pas pu être évaluée dans l'étude 6 compte tenu de la nature du devis expérimental (une seule mesure de SMT en phase aiguë).

Enfin, l'étude 5 (revue de littérature) soulève que la SMTr apparait particulièrement pertinente comme technique d'intervention considérant sa capacité à cibler les mécanismes de la douleur, à savoir la sensibilisation centrale et la neuroinflammation, ainsi qu'à induire des effets qui perdurent dans le temps (Wassermann, 1998). En effet, il a été démontré que cette technique permet de cibler spécifiquement les réseaux nocicepteurs et de rétablir le débalancement physiologique entre l'activité GABAergique et l'activité glutaminergique (Hallett, 2000, 2007). C'est d'ailleurs en partie pour cette raison que des effets analgésiques ont été observés dans diverses conditions de douleur chronique (Galhardoni et al., 2015; Lefaucheur, Drouot, Menard-Lefaucheur, Keravel, & Nguyen, 2006; Platz, 2016). Par ailleurs, son application précoce, soit en phase aiguë post-accident, n'a jamais été explorée, mais celle-ci pourrait peut-être permettre de prévenir la transition de la douleur aiguë à la douleur chronique. L'évaluation du potentiel clinique de cette technique appliquée en phase aiguë semble d'autant plus pertinente considérant le débalancement des mécanismes d'excitabilité corticale qui a été détecté dans le cadre de l'étude 6. Ainsi, les études futures permettront d'établir si cette technique s'avère utile pour contrebalancer le déséquilibre des mécanismes d'excitabilité corticale observé chez les sujets souffrant de douleur aiguë d'intensité modéré à sévère.

Limites

Les études de cette thèse comportent des limites. Cette section abordera d'abord les limites générales, communes à l'ensemble des études de la thèse. Ensuite, il sera question des limites plus spécifiques découlant de chaque étude.

Limites générales

En termes de limites générales, notons d'abord que l'ensemble des données cliniques (étude 1, 2, 3, 4 et 6) émane d'un seul centre hospitalier, ce qui limite la généralisation des résultats à d'autres milieux hospitaliers. Ceci est surtout problématique pour la première étude dont l'un de ses objectifs était de déterminer le taux de TCCL non diagnostiqué chez une population consultant au DU pour une fracture. Il est connu dans la littérature que les mesures mises en place pour identifier les TCCL varient entre établissements (Haydel, 2012). Dans ce contexte, il est possible que le taux de TCCL non diagnostiqué obtenu dans l'étude 1 ne soit pas représentatif de la situation retrouvée dans d'autres institutions médicales, surtout hors Québec. En effet, le Québec peut compter sur des lignes directrices claires, émises par l'INESSS, entourant le dépistage et la prise en charge des TCCL, ce qui peut réduire l'hétérogénéité dans les mesures déployées au sein des différents établissements québécois (INESSS, 2018). De plus, les données des études 1 à 4 proviennent du même échantillon de patients. Ainsi, il serait pertinent de recueillir les mesures de ces études au sein d'autres échantillons afin de vérifier la reproductibilité des résultats et d'augmenter la possibilité de généraliser nos observations. Rappelons que l'absence d'identification précoce, voire totale, de TCCL augmente significativement les risques de chronicisation de l'état clinique (Ponsford et al., 2002; Wade et al., 1998). Or, l'étude 1 a démontré qu'une large proportion de TCCL n'avait pas été dépistée au sein de notre échantillon, rendant ces patients à plus haut risque de se chroniciser. Ainsi, le profil clinique dressé dans les études 2, 3, 4 est possiblement teinté par l'absence de dépistage précoce, sachant qu'il s'agit du même échantillon de patients que pour l'étude 1. Il est possible que les résultats obtenus dans ces études conviennent à un sous-groupe de la population aux prises avec une fracture et un TCCL, limitant la généralisation. Il serait intéressant, dans le cadre d'études futures, de comparer les résultats cliniques recueillis dans la présente thèse à ceux découlant d'une cohorte de patients similaires, mais ayant reçu le diagnostic de TCCL précocement. Enfin, pour l'ensemble des études de cette thèse, le délai écoulé entre l'accident et la cueillette de données n'était pas homogène entre les participants. Bien qu'un effort ait été investi afin de limiter l'impact possible de cette variabilité interindividuelle, il n'en demeure pas moins que les fractures et les TCCL sont deux conditions cliniques qui évoluent rapidement et différemment chez les personnes qui en sont

atteintes. Un suivi longitudinal instauré dès les premiers jours post-accident, avec des temps de mesure communs pour tous les sujets apparait particulièrement important.

Limites de l'étude 1

La limite principale de la première étude est le fait d'avoir utilisé des données majoritairement autorapportées provenant d'un témoignage effectué en moyenne 4,12 mois post-accident. Puisque cette étude visait à recueillir des informations à propos de l'accident (mécanismes d'accident, symptômes cliniques, etc.), la possibilité d'un biais de réponse ne peut être écartée. Lorsque possible, des démarches ont été entreprises afin de corroborer les propos des patients par des membres de l'entourage. De même, les dossiers médicaux ont été consultés afin d'appuyer les données obtenues à partir des entrevues cliniques.

Limites de l'étude 2

La deuxième étude, qui visait à mesurer le niveau de douleur ressentie, ne renferme aucune information sur la médication analgésique ingérée par les patients au moment de la cueillette de données. Ceci s'avère une limite considérant la mesure d'intérêt principale de l'étude, soit l'intensité de la perception de douleur. En effet, la prise de médicament, ou non, lors de l'administration du questionnaire peut influencer le degré de la douleur perçue et donc, avoir créé des disparités non-mesurées au sein de l'échantillon. De plus, des études ont démontré que l'absence d'un traitement analgésique optimal en phase aiguë pour dissiper les symptômes douloureux post-fracture peut avoir des effets néfastes au long cours sur les plans physiques et psychologiques, dont le maintien de symptômes douloureux (Brown, Klein, Lewis, Johnston, & Cummings, 2003; Ahmadi et al., 2016). Or, dans le contexte de l'étude 2, il n'a pas été possible d'identifier la proportion des participants ayant bénéficié d'un traitement optimal des symptômes douloureux, notamment via l'administration de médicaments analgésiques. Ainsi, il est possible que le niveau de douleur rapporté par les participants puisse avoir été interprété à tort comme découlant du TCCL, plutôt que de l'efficacité du traitement administré aux participants. Cette limite découle du fait que les données de l'étude 2 ont été recueillies dans le cadre de l'étude 1 (dépistage de TCCL) dont la cueillette de données a été effectuée, pour la plupart des participants, plusieurs mois post-accident. Ainsi, un retraçage rétrospectif de la prise

de médication depuis l'accident n'était pas possible ni fiable. Ainsi, l'homogénéité intra et intergroupe au niveau de la prise de médicaments analgésiques ne peut être garantie. L'absence de contrôle de ce facteur est problématique, surtout considérant la nature de l'étude qui s'intéressait spécifiquement à la perception de douleur chez l'échantillon d'individus recrutés. De plus, cette étude n'a pas recueilli de mesures permettant d'estimer l'état psychologique des patients. Ceci est une limite importante considérant l'implication reconnue de la sphère psychologique dans la perception de douleur, soit une mesure entièrement subjective (Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Vranceanu et al., 2014). En plus de l'ajout de mesures psychologiques, il aurait pu être pertinent d'inclure des mesures additionnelles de douleur reconnues comme étant davantage objectives, tel le paradigme appelé « conditioned pain modulation, » afin d'appuyer les données autorapportées. En effet, le paradigme « conditioned pain modulation » est une mesure psychophysique objectivement fiable de la voie endogène inhibitrice de la douleur qui reflète la conduction nociceptive (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016).

Limites de l'étude 3

La troisième étude reposait sur deux mesures de retour au travail : 1) retour au travail effectué ou pas; 2) délai entre l'accident et la date du retour au travail. Par contre, des mesures additionnelles permettant de mieux cerner l'efficience lors du retour au travail auraient été pertinentes afin de dresser un portrait plus complet de la situation (Besoin d'apporter une modification aux tâches ? Fonctions et responsabilités au travail sont-elles conformes à celles avant l'accident? Changement de poste? Retour progressif, temps partiel, temps plein? Etc.). De plus, d'autres mesures dont l'état psychologique, le niveau d'éducation, le degré de catastrophisation ainsi que la présence, ou non, d'une intervention chirurgicale, n'ont pas été recueillies, mais mériteraient de l'être dans des études futures en raison de leur impact sur la mesure d'intérêt, soit le retour au travail (Das De, Vranceanu, & Ring, 2013; Drake, Gray, Yoder, Pramuka, & Llewellyn, 2000; Shi, Sinden, MacDermid, Walton, & Grewal, 2014).

Limites de l'étude 4

Une limite de l'étude 4 est d'avoir utilisé le retour au travail comme unique mesure pour estimer l'impact clinique de la formation d'ossification hétérotopique. D'autres mesures cliniques, soit l'état fonctionnel ou l'intensité de douleur, auraient permis de mieux comprendre l'impact fonctionnel de l'ossification hétérotopique ainsi que le lien entre l'ossification hétérotopique et le retour au travail. En effet, dans l'étude 4, la majorité des cas d'ossification hétérotopique a été jugée de bas grade selon l'échelle de classification de Brooker et Della Valle. Le retour au travail comme mesure fonctionnelle unique ne permet pas de déterminer de quelle façon l'ossification hétérotopique interfère avec le fonctionnement de la personne atteinte (L'OH occasionne-t-elle de la douleur ? une perte d'amplitude articulaire ? une diminution de la force motrice ? Etc.). De plus, il aurait été pertinent d'inclure d'autres mesures dont la durée de l'immobilisation, la présence d'antécédents d'ossification hétérotopique et la prédisposition génétique à une telle affection médicale, trois facteurs de risque de cette condition (Dizdar et al., 2013; Pape, Marsh, Morley, Krettek, & Giannoudis, 2004). Cela aurait permis de mieux cerner l'impact réel du TCCL sur l'ossification hétérotopique. Enfin, il faut tenir compte d'un biais possible au sein des résultats de cette étude considérant l'établissement de soins où les données ont été recueillies, soit dans un centre tertiaire de traumatologie. Par exemple, il est possible qu'une proportion de patients faisant partie de notre échantillon ait été référée à la clinique d'orthopédie de l'HSCM par d'autres cliniques pour bénéficier de soins plus spécialisés considérant l'ampleur de leur problématique. C'est donc dire que le profil de patients formant l'échantillon de l'étude 4 peut en être un aux prises avec une problématique plus sévère que la population générale ayant subi une fracture isolée et donc, plus à risque de complications. Notons également que la découverte de signes d'OH, surtout de grade léger, dépend étroitement de la durée du suivi et du recours aux examens radiologiques. En d'autres termes, il est possible que les participants de l'échantillon aient été soumis à un examen radiologique de routine pour vérifier la consolidation de l'os sans qu'aucun signe clinique ne piste le clinicien vers l'hypothèse de complications orthopédiques (dont l'OH). Chez certains patients, les signes d'OH de grade léger identifiés dans l'étude 4 auraient pu passer sous le silence, surtout chez les sujets Fx sans TCCL, pour qui l'impact fonctionnel de la présence d'OH semblait minimal (n'a pas entrainé de délai de retour au travail).

Limites de l'étude 5

En ce qui a trait à l'étude 5, celle-ci est une revue narrative plutôt qu'une revue systématique de la littérature. Ainsi, la possibilité d'un biais au niveau de la sélection d'articles ne peut être écarté.

Limites de l'étude 6

Enfin, plusieurs limites méritent d'être soulevées concernant l'étude 6. D'abord, cette étude utilise un nombre restreint de mesures d'excitabilité corticale, ce qui limite le profil d'excitabilité corticale pouvant être dressé. D'autres mesures permettant d'investiguer l'intégrité du système GABAergique et glutaminergique sont reconnues dans la littérature et seront présentées dans la section à venir traitant d'études futures. Ensuite, la prise de médicaments de type analgésique n'a pas été contrôlée lors de la cueillette de données dans un souci de ne pas interférer avec la gestion de la douleur et pour assurer le confort chez les participants. L'absence de contrôle de ce facteur a toutefois pu mener à une variabilité interindividuelle au sein de l'échantillon. Dans ce contexte, les effets potentiels des médicaments analgésiques sur les mesures d'excitabilité corticale ne peuvent être exclus, bien qu'il existe peu d'évidences dans la littérature à cet effet (Mauger & Hopker, 2013; Ziemann, 2004). Ceci a toutefois pu influencer les mesures subjectives d'intensité de douleur et de degré d'atteinte fonctionnelle recueillies par l'entremise de questionnaires. Enfin, une autre limite de cette étude est la variabilité au sein de notre échantillon au niveau de l'hémisphère stimulé, en dépit des recommandations de comités internationaux sur la SMT qui soulignent l'importance que tous les sujets d'une étude soient stimulés du même côté (Civardi, Cavalli, Naldi, Varrasi, & Cantello, 2000; Hammond, Faulkner, Byrnes, Mastaglia, & Thickbroom, 2004). En effet, l'hémisphère stimulé variait selon l'emplacement de la blessure, soit le côté correspondant au cortex moteur primaire controlatéral à la blessure. Sur la base d'études antérieures (Moisset, de Andrade, & Bouhassira, 2015), nous avons opté pour ce critère afin de cibler précisément les mécanismes périphériques et centraux découlant de la blessure orthopédique survenue à distance de la tête. Dans un souci de contrôler ce facteur confondant, un contrôle statistique a été effectué, mais n'a révélé aucune différence interindividuelle selon le côté stimulé au niveau du profil d'atteintes d'excitabilité corticale.

Perspectives futures

De cette thèse, il se dégage de nombreuses opportunités de recherche futures qui seront abordées dans la présente section. Des recommandations à la pratique clinique actuelle seront également présentées à la lumière des résultats de la thèse.

Généralisation des résultats et mesures à prendre pour améliorer le dépistage de TCCL

D'abord, il pourrait s'avérer pertinent de reproduire la première étude au sein d'autres établissements au Québec afin de faire le point sur le taux de TCCL non diagnostiqués chez la population orthopédique. Cette démarche servira notamment à mettre en place des ressources qui sont adaptées à la réalité des institutions québécoises. Il demeure également primordial de continuer à investir des efforts afin d'améliorer le dépistage de TCCL au sein de la population. À cet effet, en contexte de fracture isolée, il est fréquent que les orthopédistes soient les seuls médecins impliqués dans les suivis du patient en phase de récupération (suivre l'état de la consolidation osseuse, contrôle de la douleur et post-chirurgie, etc.). Ils peuvent donc avoir un rôle primordial dans l'identification des symptômes liés au TCCL n'ayant pas été décelés au DU (Uhl, Rosenbaum, Czajka, Mulligan, & King, 2013). Des efforts devraient être déployés afin de sensibiliser les orthopédistes à cette réalité ainsi qu'à les outiller dans la reconnaissance des symptômes et dans la marche à suivre lorsqu'il y a suspicion de TCCL (p.ex. : référence vers le médecin de famille ou l'équipe de neurotraumatologie).

Ajout de mesures objectives et subjectives afin de caractériser plus finement le profil de récupération de la population d'intérêt

L'introduction de mesures objectives, dont le dynamomètre (mesure de la force motrice) et le goniomètre (mesure de l'amplitude articulaire), deux outils couramment utilisés en recherche, devrait être considérée afin de suivre l'évolution de la fonction motrice des patients récupérant d'une fracture (McKee et al., 2006). Des déficits au niveau de ces mesures ont également été objectivés chez des cohortes de TCCL (Evans et al., 2012; Miller et al., 2014). Ainsi, il pourrait s'avérer intéressant d'avoir recours à ces mesures pour étudier le profil de récupération de la

fonction motrice selon la présence, ou non, d'un TCCL concomitant à une fracture. Ensuite, des liens entre les mesures subjectives de l'état fonctionnel et celles davantage objectives pourront être effectués.

De plus, il pourrait être intéressant de mesurer d'autres facteurs susceptibles d'être altérés en contexte de TCCL et de fracture. D'abord, le volet psychosocial ne devrait pas être écarté. Il est connu que le TCCL et la fracture génèrent, de manière indépendante, des conséquences collatérales au plan psychosocial, telles que des symptômes anxio-dépressifs, un sentiment d'isolement et des difficultés d'adaptation (Vikane et al., 2016). De manière similaire, les troubles du sommeil post-TCCL, post-fracture ou en contexte de douleur sont également prévalents (Herrero Babiloni, Guay, Nixdorf, De Beaumont, & Lavigne, 2018; Wickwire et al., 2016). Il pourrait s'avérer pertinent d'étudier le lien entre ces différents facteurs (TCCL, fracture et douleur) et la qualité de sommeil des patients, surtout qu'une piètre qualité de sommeil peut, à son tour, entraver la récupération dont l'efficience de la consolidation osseuse (Swanson et al., 2018) et faciliter le développement de douleur (Sutton & Opp, 2014; Vanini, 2016). De plus, il serait important d'explorer l'impact du temps écoulé entre l'accident et la chirurgie réalisée et la récupération fonctionnelle des patients fracture+TCCL. En effet, des études réalisées chez la population avec traumatismes combinés (multiples traumas orthopédiques et TCC modéré/sévère) ont montré que la fenêtre temporelle entre l'accident et la chirurgie était un élément qui pouvait influencer la récupération des patients et qui devrait donc être pris en considération (Lu et al., 2020). Plus spécifiquement, une étude a démontré qu'une chirurgie effectuée plus de 14 jours post-accident augmentait le risque de complications, dont des signes de non-union et de mal-union (Lu et al., 2020). De plus, Lu et collègues (2020) ont soulevé l'hypothèse que la chirurgie effectuée en périphérie peut provoquer des séquelles au cerveau déjà fragilisé par le TCC, en augmentant notamment les risques d'hypoxie, la réponse inflammatoire et l'hypotension cérébrale. Par ailleurs, il n'existe pas d'études à ce jour qui se sont penchées sur les délais chirurgicaux à respecter en contexte de blessures de sévérité plus légère. Ceci pourrait être pertinent afin d'optimiser la récupération de cette population.

Quel est l'impact de la fracture sur la récupération d'un TCCL?

Les études de cette thèse ont investigué, de manière quasi-unilatérale, l'impact du TCCL sur la fracture. L'approche inverse serait également très pertinente, soit d'investiguer l'impact d'une fracture sur le rétablissement post-TCCL. Il existe actuellement quelques données probantes qui suggèrent que la présence de blessures extra-crâniennes augmenterait le risque de développer un syndrome post-commotionnel chez des personnes avec TCCL (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010; Jacobs et al., 2010; Prigatano & Gale, 2011; Stulemeijer et al., 2008; Tator et al., 2016). Ce lien a toutefois été remis en question dans une étude publiée par Dischinger et collègues (2009), une discordance qui pourrait s'expliquer par la variabilité quant à la nature des blessures extra-crâniennes (fracture, contusion, lacération, atteinte à un organe, entorse, etc.) incluses au sein des études. Ainsi, il serait pertinent d'étudier spécifiquement l'impact d'une fracture sur l'intensité des symptômes post-commotionnels et le risque de développer un syndrome post-commotionnel. Par ailleurs, les TCCL peuvent induire des séquelles cognitives, tant en phases aiguë que chronique, pouvant être décelées à partir d'outils neuropsychologiques. Les lacunes cognitives touchent généralement la vitesse de traitement de l'information, les capacités d'apprentissage, la mémoire, l'attention et certaines fonctions exécutives (Rabinowitz & Levin, 2014). Pertinemment, la douleur et la cognition partagent des mécanismes communs et peuvent s'influencer mutuellement (Moriarty & Finn, 2014; Moriarty, McGuire, & Finn, 2011). En contexte de TCCL, la douleur peut exacerber les difficultés cognitives découlant du TCC (Beaupre, De Guise, & McKerral, 2012; Kjeldgaard, Forchhammer, Teasdale, & Jensen, 2014). Il pourrait donc s'avérer pertinent de suivre l'évolution de diverses fonctions cognitives, à l'aide de tests neuropsychologiques, chez la population avec fracture selon la présence, ou non, d'un TCCL. L'intensité de la douleur au moment de la cueillette de données devrait également être prise en compte tout comme la prise de médicaments analgésiques, facteurs pouvant altérer la cognition (Moriarty et al., 2011).

Pertinence des suivis longitudinaux et d'un accès à des services multidisciplinaires

Cette thèse ne permet pas d'effectuer des comparaisons dans le temps des mesures d'intérêt au sein des participants (un seul temps de mesure). De même, seules des données issues la phase post-aiguë ont été recueillies. Ainsi, il serait intéressant de réaliser des études suivant les patients longitudinalement afin d'identifier lesquels récupéreront normalement ou, à l'opposé, développeront une condition chronique. Par exemple, un suivi longitudinal couvrant la phase chronique de récupération permettra de déterminer le taux de SDRC, type de douleur chronique pour lequel les gens souffrant de fracture sont particulièrement à risque (Guthmiller & Varacallo, 2018). Il sera intéressant d'investiguer si le SDRC est plus prévalent chez les patients fracture+TCCL, sachant qu'un TCCL peut, à lui seul, provoquer ce type de complications (Park et al., 2009). Il serait également intéressant de se pencher sur les perturbations aiguë et chronique de la qualité du sommeil, particularités souvent sous-rapportées et auxquelles les populations souffrant de TCCL, de fractures ou de douleur, sont à risque (Menefee et al., 2000; Mollayeva, Mollayeva, & Colantonio, 2016; Shulman, Liporace, Davidovitch, Karia, & Egol, 2015). Devant l'évidence qu'une piètre qualité de sommeil peut nuire au rétablissement post-trauma (Swanson et al., 2018) et peut demeurer problématique plusieurs années post-accident (Theadom et al., 2015), il serait pertinent d'établir le profil nocturne des patients aux prises avec un double traumatisme (TCCL+fracture) afin de mettre en place les ressources nécessaires pour maximiser la récupération. À titre d'exemples, un journal de sommeil introduit dès la phase aiguë est facilement accessible, sollicitant peu de ressources tout en étant une source riche d'informations. En parallèle, l'utilisation de mesures davantage objectives, telles la polysomnographie ou l'imagerie cérébrale, pourrait être considérée lors d'études futures. Une panoplie d'autres indicateurs de chronicisation précédemment évoqués pourront être investigués grâce aux suivis longitudinaux (syndrome post-commotionnel, non union/mal union, état psychologique, etc.).

Au-delà du contexte de recherche, la réalité clinique de cette population justifie également qu'un suivi longitudinal soit disponible au besoin afin de limiter le risque de chronicisation. Ainsi, outre l'équipe médicale, l'expertise d'autres professionnels de la santé pourraient être sollicitée, dont celle des physiothérapeutes. En effet, les physiothérapeutes sont quasi-systématiquement

impliqués, lorsque les ressources le permettent, dans le plan de traitement post-fracture afin d'améliorer la récupération de la fonction motrice (A. Bruder, Taylor, Dodd, & Shields, 2011; A. M. Bruder, Shields, Dodd, & Taylor, 2017). Plus récemment, il y a une reconnaissance grandissante de leur expertise dans le traitement du TCCL (Quatman-Yates et al., 2020), faisant d'eux des experts à considérer pour suivre l'évolution de patients présentant à la fois une fracture et un TCCL. De plus, une implication plus sporadique des psychologues et des neuropsychologues devrait être considérée, selon le besoin. En effet, l'impact psychologique découlant d'un accident aux éléments, pour certains patients, traumatiques ainsi que des impacts collatéraux de subir une fracture (isolement social, vivre avec de la douleur et perte d'autonomie, etc.) et un TCCL ne peut être minimisé. De même, en cas de suspicions de difficultés cognitives, de plaintes cognitives subjectives ou de simulation suspectée, une évaluation neuropsychologique pourrait être réalisée pour porter un éclairage sur la situation.

Caractérisation plus approfondie des mécanismes d'excitabilité corticale

Il existe d'autres protocoles de SMT qui n'ont pas été utilisés dans l'étude 6. Ainsi, l'ajout de mesures additionnelles d'excitabilité corticale du cortex moteur primaire pourrait permettre d'approfondir notre compréhension de l'impact de la douleur aiguë sur les mécanismes d'excitabilité corticale. Par exemple, les protocoles mesurant l'inhibition afférente à courte latence (IACL) et l'inhibition afférente à longue latence (IALL) devraient être intégrés dans les études futures. En effet, ces protocoles permettent de mesurer l'intégrité de l'intégration sensorimotrice, soit la communication entre la voie sensorielle ascendante et la voie motrice descendante (Turco et al., 2018). Une altération de l'intégration sensorimotrice a été identifiée dans diverses conditions de douleur chronique, dont le SDRC (Daenen et al., 2013; McCabe, Haigh, Halligan, & Blake, 2005). Par ailleurs, on ne détient aucune connaissance au niveau des mécanismes d'intégration sensorimotrice en contexte de douleur aiguë. Ainsi, l'ajout de ces mesures de SMT serait complémentaire à celles déjà recueillies dans l'étude 6, lesquelles ont seulement permis d'investiguer l'intégrité du système moteur, soit la voie descendante. De plus, il serait pertinent d'instaurer un suivi longitudinal de mesures d'excitabilité corticale assurant la couverture des phases aiguë et chronique de la récupération. Cela permettrait de mieux comprendre l'implication à long terme des perturbations des systèmes GABAergique et

glutaminergique identifiées en phase aiguë dans l'étude 6. En contexte d'études longitudinales, il sera important de considérer l'impact connu d'une immobilisation prolongée du membre atteint sur les mesures d'intérêt, notamment l'excitabilité corticale (Clark, Taylor, Hoffman, Dearth, & Thomas, 2010; Langer, Hanggi, Muller, Simmen, & Jancke, 2012; Liepert, Tegenthoff, & Malin, 1995). De plus, il serait pertinent de reproduire le protocole utilisé dans l'étude 6 en incluant une cohorte de sujets présentant à la fois une fracture et un TCCL. En effet, on retrouve dans la littérature des études s'étant penchées sur l'impact distinct d'une fracture ou d'un TCCL sur l'excitabilité corticale, mais cela n'a, à ce jour, pas été fait en contexte de blessures combinées. Il est possible que le profil d'atteintes sur le plan des mécanismes d'excitabilité corticale diffère selon la présence, ou non, d'un TCCL. Enfin, des études futures ayant recours à la SMT pourraient considérées investiguer le fonctionnement d'autres régions cérébrales, dont le cortex préfrontal dorsolatéral (DLPFC). Le DLPFC est une région du cerveau qui occupe diverses fonctions notamment impliquées dans le traitement cognitif, affectif et sensoriel (Glasser et al., 2016). Des altérations au niveau du DLPFC ont été démontrées chez diverses populations dont celles avec TCCL (Lipton et al., 2009) ainsi que celles aux prises avec de la douleur chronique (Seminowicz & Moayedi, 2017), mais cela n'a jamais été fait en contexte de blessures combinées (TCCL et fracture isolée). Des liens entre les mesures de SMT et cliniques (degré de douleur, symptômes psychologiques et cognitifs) pourraient apporter un nouvel éclairage.

Interventions et traitement contre la douleur : comment limiter l'utilisation des opioïdes?

Il existe un problème sociétal majeur entourant le traitement de la douleur. En 2001, le Joint Commission on Accreditation of Healthcare Organization a établi que la détection et le traitement précoce de la douleur devraient être considérés comme élément standard à la pratique médicale d'aujourd'hui, notamment dans l'optique de diminuer les coûts onéreux associés à un rétablissement plus long. Depuis, des traitements pharmacologiques, dont les anti-inflammatoires non stéroïdiens (AINS) et les opiacés, sont administrés au DU afin d'atténuer rapidement, quasi instantanément, la douleur rapportée par les patients (Majuta et al., 2015; Rupp & Delaney, 2004). Plus spécifiquement, la prescription d'opioïdes demeure le traitement le plus couramment utilisé pour diminuer la douleur (Chaudhary et al., 2017). Ses effets

analgésiques servent à diverses populations, que ce soit pour les patients traités pour un cancer ou pour de la douleur chronique. Cette molécule a causé des dommages considérables sur la santé des consommateurs, allant de la dépendance jusqu'à la mort, obligeant les différents pays à se positionner face à ce fléau. En effet, les risques de développer une dépendance en lien avec la consommation d'opioïdes sont élevés, avec comme principale source, la prescription médicale (Cicero, Ellis, Surratt, & Kurtz, 2014). Un comité de législateurs américains a d'ailleurs limité à sept jours la durée de la prescription initiale d'opioïdes chez de nouveaux bénéficiaires (Lowenstein, Grande, & Delgado, 2018). Une quantité croissante d'études remettent en question son utilisation (Gessner et al., 2019) et illustrent un besoin criant de développer d'autres alternatives thérapeutiques pour traiter la douleur. D'autres méthodes moins connues ont été conçues dans le but de traiter les douleurs persistantes chez les patients orthopédiques en occasionnant moins d'effets secondaires. Parmi celles-ci, la SMTr offre une alternative intéressante et non invasive dans le traitement de la douleur chronique. Tel qu'évoqué dans l'étude 5, cette technique permet notamment d'intervenir sur l'équilibre neuronal dans le but de rétablir un certain débalancement cérébral. Plus spécifiquement à la douleur chronique, il a été suggéré que la STMr permettrait de moduler l'activité nociceptive du cerveau reliée au système opioïde endogène, impliqué dans la perception de la douleur (Moisset et al., 2015). Par exemple, il a été démontré que la SMTr procure des effets analgésiques, comparables à ceux procurés par les AINS et les opiacés, sans toutefois être associée à de nombreux effets secondaires indésirables. Au-delà de cette technique de stimulation, d'autres approches non-pharmacologiques aux effets secondaires limités pourraient être envisagées pour réduire l'usage de narcotiques. Parmi celles-ci, il y a l'exercice physique. En effet, au-delà des effets bénéfiques bien connus sur la santé en général, l'exercice physique a également fait ses preuves dans le traitement contre la douleur autant au sein d'études précliniques que cliniques (Ambrose & Golightly, 2015; Mazzardo-Martins et al., 2010). L'utilisation de ce type d'intervention a même été démontrée comme méthode pouvant prévenir la transition de la douleur aiguë vers la douleur chronique (Sluka, O'Donnell, Danielson, & Rasmussen, 2013). Les effets thérapeutiques découlant de l'exercice physique en contexte de douleur s'expliqueraient par la convergence de multiples facteurs, dont l'activation des systèmes opioïde endogène et sérotoninergique (Mazzardo-Martins et al., 2010) et la réduction de

l'activation d'une sous-propriété des récepteurs NMDA impliqués dans la perception de douleur (Sluka et al., 2013). En plus de ses effets analgésiques, ce type d'intervention est déjà utilisé au sein de populations avec TCCL ou fractures et ses effets bénéfiques semblent se généraliser à d'autres types de mesures cliniques (p.ex. : prévient le déconditionnement, améliore l'humeur et l'état cardiovasculaire, brise l'isolement social si réalisé en contexte de groupe, réduit les symptômes post-commotionnels) (Karlsson, Nordqvist, & Karlsson, 2008; Latham et al., 2014; Leddy & Willer, 2013; Tan, Meehan, Iverson, & Taylor, 2014). Dans ce contexte, il serait intéressant d'évaluer les effets de cette technique sur plusieurs mesures cliniques chez des patients avec fracture+TCCL. Les études futures devront se concentrer à établir le protocole optimal (fréquence, durée, intensité, quand l'introduire post-accident) et à surveiller l'intensité des symptômes, car l'introduction trop précoce de ce type d'intervention peut devenir un vecteur exacerbant l'intensité de certains symptômes.

Enfin, des évidences scientifiques soulèvent qu'un patient qui perçoit positivement l'équipe médicale sera plus porté à s'investir dans les démarches de guérison. En effet, l'alliance thérapeutique peut étroitement influencer le degré d'investissement (Stagg, Douglas, & Iacono, 2019). Des études futures qui offrent un protocole d'intervention et un suivi étroit auprès des patients devraient donc inclure des mesures permettant d'apprécier ce phénomène, soit la façon dont le patient perçoit la prise en charge, afin d'évaluer son impact sur la récupération fonctionnelle (perception de douleur, durée du retour au travail, quantité de symptômes auto-rapportés etc.). En contexte d'intervention, comme dans un protocole de SMTr ou d'exercice physique qui comprend deux groupes (SHAM et actif), cela pourrait permettre d'investiguer la présence d'un effet placebo selon la perception du patient vis-à-vis l'équipe de recherche qui assure un suivi étroit et longitudinal. À cet égard, il pourrait également s'avérer pertinent d'inclure un troisième groupe évalué à une reprise, soit en phase chronique, et qui obtient un suivi minimal par les intervenants afin de mieux apprécier le phénomène d'effet placebo.

Conclusion

En conclusion, la présente thèse comprenait deux volets généraux. Le premier volet avait pour objectif d'investiguer l'incidence de TCCL concomitant à une fracture isolée ainsi que son impact

sur la récupération orthopédique, soit au niveau de la perception de douleur, du délai nécessaire pour retourner au travail et du risque de développer de l'ossification hétérotopique. Le deuxième volet s'intéressait plus spécifiquement aux mécanismes physiologiques décelés après une fracture qui est accompagnée, ou non, de blessures traumatiques, en adoptant une approche clinique et théorique. Ainsi, cette thèse inclut six articles scientifiques. Dans un premier temps, les résultats de la présente thèse soulèvent l'importance d'investir des ressources afin de réduire le taux de TCCL non dépisté chez la population aux prises avec une fracture. L'impact du TCCL sur la récupération orthopédique est non négligeable selon les résultats de la thèse, pouvant augmenter l'intensité de la douleur perçue, le délai pour retourner au travail et le risque de développer de l'ossification hétérotopique. Des suivis longitudinaux auprès de patients récupérant d'une fracture et d'un TCCL concomitant seront importants afin de suivre étroitement leur évolution et de réduire les risques de chronicisation. Dans un deuxième temps, la présente thèse a démontré une atteinte des mécanismes d'inhibition et de facilitation intracorticale du cortex moteur primaire chez des patients avec fracture qui rapportaient un niveau de douleur modéré à sévère en phase aiguë. Il faudra déterminer, dans le cadre d'études futures, si l'altération des mécanismes d'excitabilité corticale en phase aiguë est un précurseur au développement de la douleur chronique. Dans de tels cas, une intervention précoce à l'aide de la SMTr pourrait permettre de rétablir l'équilibre des mécanismes d'excitabilité corticale considérant sa capacité à cibler des mécanismes physiologiques clés. En somme, les résultats de l'ensemble des articles de cette thèse sont un ajout intéressant à la littérature qui s'est à présent davantage consacrée à étudier l'impact combiné d'un TCC et de TO en contexte de blessures jugées plus sévères. Ces études comprennent toutefois des limites qui ont été discutées et qui devraient être abordées dans le contexte d'études futures afin d'obtenir un portrait plus exhaustif de la situation au sein de cette population.

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